Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2602

icosapent ethyl soft capsules (Vazkepa®)

Amarin Pharma Inc

07 July 2023

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a resubmission

icosapent ethyl (Vazkepa®) is accepted for restricted use within NHSScotland.

Indication under review: to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥1.7mmol/L) and

• established cardiovascular disease, or

• diabetes, and at least one other cardiovascular risk factor.

SMC restriction: use as secondary prevention in patients treated with a stable dose of statins, low-density lipoprotein (LDL) cholesterol levels >1.04mmol/L and ≤2.60mmol/L, raised fasting triglycerides (≥1.7mmol/L) and with established cardiovascular disease defined as a history of any of the following:

- Acute coronary syndrome (ACS) (such as myocardial infarction (MI) or unstable angina needing hospitalisation)
- Coronary or other arterial revascularisation procedures
- Coronary heart disease
- Ischaemic stroke
- Peripheral arterial disease

In a phase III study, icosapent ethyl significantly reduced the risk of major adverse cardiovascular events in statin-treated patients at high-risk of cardiovascular events with elevated triglycerides, compared with a mineral oil placebo.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Vice Chair
Scottish Medicines Consortium

Clinical Context

Medicine background

Icosapent ethyl is an ester of the omega-3 fatty acid, eicosapentaenoic acid (EPA). The mechanisms of action that contribute to reduction of cardiovascular events with icosapent ethyl are not completely understood but are likely to be multi-factorial and may include an improved lipoprotein profile with a reduction of triglyceride-rich lipoproteins, anti-inflammatory, and antioxidant effects, a reduction of macrophage accumulation, improved endothelial function, increased fibrous cap thickness or stability and antiplatelet effects.[1]

Disease background

Cardiovascular disease encompasses a range of conditions including coronary heart disease, cerebrovascular disease and peripheral arterial disease. It is one of the leading causes of mortality in Scotland, with 17,639 cardiovascular disease deaths reported in 2021. It is more prevalent in men, people aged over 50 years, certain ethnic backgrounds and in areas of high deprivation. Common modifiable risk factors include hypertension, high total cholesterol, diabetes mellitus, smoking, obesity and physical inactivity. Hypertriglyceridaemia is an independent risk factor for cardiovascular disease and is associated with fasting triglyceride levels ≥1.7mmol/L.[2-6]

Company proposed position

The submitting company has requested that SMC consider icosapent ethyl for use as secondary prevention in patients treated with a stable dose of statins, low-density lipoprotein (LDL) cholesterol levels >1.04mmol/L and ≤2.60mmol/L, raised fasting triglycerides (≥1.7mmol/L) and with established cardiovascular disease defined as a history of any of the following:

- Acute coronary syndrome (ACS) (such as myocardial infarction (MI) or unstable angina needing hospitalisation)
- Coronary or other arterial revascularisation procedures
- Coronary heart disease
- Ischaemic stroke
- Peripheral arterial disease

Treatment pathway and relevant comparators

In patients with established cardiovascular disease, secondary prevention with intensive statin therapy is recommended as first-line lipid lowering treatment to reduce the risk of coronary heart disease and stroke. Lifestyle modifications including diet, exercise and smoking cessation are advised and the treatment of underlying conditions such as diabetes mellitus should be optimised. The addition of ezetimibe can be considered if LDL cholesterol is inadequately controlled despite maximum tolerated statin therapy. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors may also be considered in combination with lipid lowering therapies if LDL cholesterol goals are not reached however they have been accepted by SMC for restricted use only by specialists and in a small selected population of patients at high cardiovascular risk (SMC1147/16, SMC1148/16 and SMC2358). Although fibrates are not routinely recommended for secondary prevention, they may be used for patients with severe hypertriglyceridaemia who have cardiovascular disease, or who are at high cardiovascular risk, and have low high-density lipoprotein (HDL) cholesterol. European

guidelines recommend that a fibrate may be considered in combination with a statin in high risk patients at their LDL cholesterol goal with triglyceride levels >2.3mmol/L. There is no SMC advice for fibrates as the medicines were initially licensed and made available to the market prior to the inception of SMC. Fibrates are also used in severe hypertriglyceridaemia to reduce the risk of acute pancreatitis.[2, 5] SMC clinical experts indicated that in clinical practice, although some patients with elevated triglycerides may receive fibrates, many patients with LDL cholesterol levels >1.04mmol/L and ≤2.60mmol/L and raised fasting triglycerides (≥1.7mmol/L) would not currently receive additional pharmacological treatment. The most relevant comparator for this submission is standard of care (SOC) with statins with or without ezetimibe. Fibrates may represent an additional comparator for a small number of patients with severe hypertriglyceridaemia.

Summary of Clinical Evidence

Evidence for the licensed indication under review

Evidence to support the efficacy and safety of icosapent ethyl is from the REDUCE-IT study. Details are summarised in Table 2.1.[4, 7]

Table 2.1. Overview of relevant studies

Criteria	REDUCE-IT[4, 7]
Study design	Multicentre, randomised, controlled, double-blind, phase IIIb study
Eligible patients	• Fasting triglyceride (TG) levels 1.53mmol/L to 5.64mmol/L: after protocol amendment in May 2013, included fasting TG levels 2.26mmol/L) to 5.64mmol/L. • LDL cholesterol levels 1.04mmol/L to 2.60mmol/L. • On stable statin treatment (this is, no change to dose within 28 days), with or without ezetimibe. • No patients had an HbA_{1c} >10% (or >86mmol/mol) or had poorly controlled hypertension **Secondary prevention subgroup (n=5,785)**: adults ≥45 years with established cardiovascular disease, including at least one of the following: • Coronary artery disease. • Cerebrovascular or carotid disease • Peripheral arterial disease. **Primary prevention subgroup (n=2,394)**: adults ≥50 years with diabetes mellitus (type 1 or type 2) requiring medical treatment and at least one of the following risk factors at baseline: • Men ≥55 years or women ≥65 years who are current smokers or stopped ≤3 months of screening. • Hypertension or on antihypertensive medication. • HDL cholesterol ≤1.03mmol/L for men or ≤1.29mmol/L for women. • hsCRP >3.0mg/L (0.3mg/dL). • Renal dysfunction (creatinine clearance >30 to <60mL/min). • Retinopathy. • Micro- or macroalbuminuria. • ABI <0.9 without symptoms of intermittent claudication.
Treatments	Oral icosapent ethyl 2 grams twice daily or mineral oil placebo.

Randomisation	Patients were randomised equally to each group. Stratification was based on cardiovascular risk subgroup (secondary or primary prevention), use of ezetimibe (yes or no) and geographic region (Western countries, Eastern European countries and Asia Pacific).
Primary outcome	A 5-point composite outcome of MACE, defined as the time from randomisation to the first occurrence of any of the following events: cardiovascular death, non-fatal MI (including silent MI), non-fatal stroke, coronary revascularisation and unstable angina requiring hospitalisation.
Secondary outcomes	• 3-point MACE composite of cardiovascular death, non-fatal MI (including silent MI) and non-fatal stroke (key secondary outcome). • Cardiovascular death or non-fatal MI. • Fatal or non-fatal MI. • Urgent or emergency revascularisation. • Cardiovascular death. • Hospitalisation for unstable angina. • Fatal or non-fatal stroke. • Total mortality, non-fatal MI or non-fatal stroke. • Total mortality.
Statistical analysis	A hierarchical statistical testing strategy was applied to the primary and key secondary outcomes (in the order listed above) in the study with no formal testing of outcomes after the first non-significant outcome in the hierarchy.
ABI=ankle brachial index; ACS=acute coronary syndrome; HbA_{1c}=haemoglobin A_{1c}; HDL=high-density lipoprotein; hsCRP=high sensitivity C-reactive protein; LDL=low-density lipoprotein; MACE=major adverse cardiovascular events; MI=myocardial infarction; TG=triglyceride	

At the primary analysis of REDUCE-IT, conducted after a median follow-up of 4.9 years, treatment with icosapent ethyl was associated with significantly fewer major adverse cardiovascular events (MACE) included in the composite primary outcome and key secondary outcome compared with placebo[4, 7] The details of the primary and key secondary outcome are presented in Table 2.2.

Table 2.2: Primary and secondary outcome results from REDUCE-IT in the ITT population.[4, 7]

	Icosapent ethyl (n=4,089)	**Placebo (n=4,090)**
Primary outcome: MACE composite of first occurrence of cardiovascular death, non-fatal MI, non-fatal stroke, coronary revascularisation and unstable angina requiring hospitalisation		
Events, n (%)	705 (17%)	901 (22%)
Hazard ratio (95% CI), p-value	0.75 (0.68 to 0.83), p<0.001	
Cardiovascular death, n (%)	137 (3.4%)	149 (3.6%)
Non-fatal MI, n (%)	205 (5.0%)	280 (6.8%)
Non-fatal stroke, n (%)	80 (2.0%)	105 (2.6%)
Coronary revascularisation, n (%)	189 (4.6%)	244 (6.0%)
Hospitalisation for unstable angina, n (%)	94 (2.3%)	123 (3.0%)

Secondary outcomes		
MACE composite of first occurrence of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke		
Events, n (%)	459 (11%)	606 (15%)
Hazard ratio (95% CI)	0.74 (0.65 to 0.83), p<0.001	
CI=confidence interval; ITT=intention-to-treat; MACE=major adverse cardiovascular events.		

Icosapent ethyl significantly reduced all other hierarchically tested secondary outcomes including cardiovascular death or non-fatal MI, fatal or non-fatal MI, urgent or emergency revascularisation, cardiovascular death, hospitalisation for unstable angina, fatal or non-fatal stroke, total mortality, non-fatal MI or non-fatal stroke. The exception was total mortality, where the between group difference was not statistically significant.[4, 7]

Pre-specified subgroup analyses for the primary outcome according to sex, geographic region, ezetimibe use, triglyceride levels and LDL cholesterol levels at baseline were generally consistent with the primary outcome analysis. However, there was a trend of lower efficacy in patients aged ≥65 years and in patients treated with a low intensity-statin dose.[4, 7]

Evidence to support the positioning proposed by the submitting company

Evidence to support the proposed positioning is from a secondary prevention subgroup of 5,785 patients with established cardiovascular disease including coronary artery disease, cerebrovascular or carotid disease, or peripheral arterial disease. For the primary and secondary composite outcomes detailed in Table 2.3, there were fewer cardiovascular events in the icosapent ethyl group compared with placebo.[4, 7]

Table 2.3: Primary and secondary outcome results from REDUCE-IT in the secondary prevention subgroup.[4, 7, 8]

	Icosapent ethyl (n=2,892)	**Placebo (n=2,893)**
Primary outcome: MACE composite of first occurrence of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation and unstable angina requiring hospitalisation		
Events, n (%)	559 (19%)	738 (26%)
Hazard ratio (95% CI)	0.73 (0.65 to 0.81)	
Component events		
Cardiovascular death, n	*	*
Non-fatal myocardial infarction, n	*	*
Non-fatal stroke, n	*	*
Coronary revascularisation, n	*	*
Hospitalisation for unstable angina, n	*	*
Secondary outcome: MACE composite of first occurrence of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke		
Events, n (%)	361 (12%)	489 (17%)
Hazard ratio (95% CI)	0.72 (0.63 to 0.82)	
CI=confidence interval; MACE=major adverse cardiovascular events; *results for the component events were considered confidential by the company.		

2.3. Health-related quality of life outcomes

No health-related quality of life outcomes were reported in REDUCE-IT.

*Other data were also assessed but remain confidential.**

Summary of Safety Evidence

The regulator noted that no major safety concerns were identified for icosapent ethyl. In the REDUCE-IT study, the median duration of treatment in the icosapent ethyl group was 4.5 years and in the placebo group was 4.2 years. Any treatment-emergent adverse event (AE) was reported by 82% (3,343/4,089) of patients in the icosapent ethyl group and 81% (3,326/4,090) in the placebo group and these were considered treatment-related in 13% and 12% respectively. In the icosapent ethyl and placebo groups respectively, patients reporting a serious AE were 31% in both groups and patients discontinuing therapy due to an AE was 7.9% and 8.2%. Treatment-emergent AEs that were more common in the icosapent ethyl group versus the placebo group included supraventricular arrhythmias (7.3% versus 5.8%), including atrial fibrillation (5.3% versus 3.9%), purine and pyrimidine metabolism disorders (5.0% versus 3.5%), including gout (4.2% versus 3.1%), rash (2.8% versus 2.0%), allergic conditions (2.4% versus 1.7%), vitamin D deficiency (2.3% versus 1.6%), and cardiac conduction disorders (2.1% versus 1.5%). The Summary of Product Characteristics (SPC) also notes that frequently reported AEs with icosapent ethyl included peripheral oedema (6.5% versus 5.0%) constipation (5.4% versus 3.6%), musculoskeletal pain (4.3% versus 3.2%) and dermatitis and eczema (3.6% versus 2.9%).[1, 4]

Icosapent ethyl has been associated with an increased risk of bleeding (12% versus 9.9%), particularly in patients taking concomitant anticoagulant or antiplatelet medication. In the REDUCE-IT study, serious bleeding events occurred in 111 patients (2.7%) in the icosapent ethyl group compared with 85 patients (2.1%) in the placebo group. The SPC notes that patients concomitantly taking antithrombotic agents should be periodically monitored. See the SPC for further safety information.[1, 7]

Summary of Clinical Effectiveness Considerations

Key strengths

- In the REDUCE-IT study, significantly fewer patients in the icosapent ethyl group had a primary outcome 5-point MACE composite event (17%) compared with the placebo group (22%), with a relative risk reduction of 25% and an absolute risk reduction of 4.8%. This was supported by a significant reduction in the key secondary outcome (3-point MACE composite) and other hierarchically tested secondary outcomes, with the exception of total mortality, in the icosapent ethyl group compared with placebo. The regulator described the key secondary outcome as the most important for assessment of efficacy and that the benefits observed were clinically relevant.[4, 7]

- In the secondary prevention subgroup of 5,785 patients that was used to support the proposed positioning, fewer patients in the icosapent ethyl group had a primary outcome event (19%), compared with the placebo group (26%). There was also a reduction in the key secondary outcome in the icosapent ethyl group compared with the placebo group.[4, 7]

Key uncertainties

- Mineral oil that was used as placebo in the REDUCE-IT study may not be truly inactive. Small numerical increases in lipid biomarkers and systolic blood pressure were observed in the placebo group that may have increased the risk of cardiovascular events and could confound study results. This may mean the control arm of REDUCE-IT is not reflective of

the standard of care in clinical practice and may overestimate the real-world effects of icosapent ethyl. The regulator noted that it is uncertain if these effects are a result of natural disease progression, variability and regression to the mean or a negative effect of the mineral oil. Analyses provided to the regulator suggest that the negative effect of the mineral oil may have accounted for up to 3% of the relative risk reduction for the key secondary outcome. This variation in effect has been explored in scenario analyses in the economic case.[4]

- Evidence to support efficacy in the proposed positioning is from a planned analysis of a secondary prevention subgroup of 5,785 patients (71% of the overall ITT population) with established cardiovascular disease. REDUCE-IT was not designed to compare subgroup populations, therefore the results are descriptive only and there is uncertainty as to the true effect size. Patients included in the secondary prevention subgroup were ≥45 years and therefore there is no evidence for the proposed positioning in younger patients.[7]
- The median duration of follow-up in the REDUCE-IT study was 4.9 years.[4, 7] Therefore the continued benefits and risks of icosapent ethyl beyond this time point are uncertain.
- The inclusion criteria for the REDUCE-IT study had an upper triglyceride threshold of <5.64mmol/L and LDL cholesterol threshold of ≤2.60mmol/L, therefore there is no evidence from REDUCE-IT in treating patients with levels beyond these thresholds. It was also unclear from the study if all modifiable lifestyle and risk factors had been adequately addressed and optimised before study entry.[7]
- REDUCE-IT did not recruit any patients from the UK. To assess the external validity of the study results, the company compared the baseline characteristics of patients in the secondary prevention subgroup of REDUCE-IT with patients in Scottish cardiovascular disease studies. In general, patients in the REDUCE-IT study were slightly older and had higher body mass index at baseline; there was also a higher prevalence of hypertension and diabetes mellitus. If patients in the study were at a higher risk of cardiovascular events than those seen in Scottish practice, this could affect the generalisability of study results. [7-12]
- There is no direct or indirect evidence comparing icosapent ethyl with a fibrate which may represent a relevant comparator for some patients with marked hypertriglyceridaemia who may be at risk of pancreatitis.[7]

Clinical expert input

Clinical experts consulted by SMC considered that icosapent ethyl may be considered for use in addition to high intensity statins for secondary prevention in the subpopulation of patients with a high-risk of a cardiovascular event.

Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Heart UK – The Cholesterol Charity, which is a registered charity.
- Heart UK – The Cholesterol Charity has received 35% pharmaceutical company funding in the past two years, including from the submitting company.
- People with CVD who already have a controlled LDL level are still at risk because of the residual risk due to other reasons, such as raised triglycerides. Living with the after effects of an event and the fear of another can affect people in many different ways, and it is not just the individual, it is the whole family. Life can be very difficult, diet and lifestyle is important but some people have challenges reducing their triglycerides overall. The extreme end of high triglycerides is hypertriglyceridaemia and this impacts daily life often with misdiagnosis.
- CVD remains the biggest killer worldwide and there is very much an unmet need in this group of patients as there are no other therapeutics available specifically for triglycerides.
- These patients are known to have heart disease and they are usually extremely fearful of another event. The individual may be managing their LDL cholesterol and other risk factors, but may not be able to manage their triglyceride level and that could cause significant anxiety for them and their family.

Summary of Comparative Health Economic Evidence

Economic case

The submitting company provided an economic case, as described in Table 6.1

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (36 years, based on an average starting age of 64)
Population	The submitting company requested that the SMC considers icosapent ethyl for use in line with the proposed position, as outlined in Section 1.3.
Comparators	Icosapent ethyl plus SOC was compared against SOC, consisting of statins, with or without ezetimibe. Statins use was modelled across low, moderate and high intensity levels, aligned with the use in the REDUCE-IT study.[7] Similarly, the level of ezetimibe use was assumed consistent with REDUCE-IT.
Model description	The economic analysis used a partitioned survival model with eight health states: cardiovascular (CV) event-free, first CV event, post-first CV event, second CV event, post-second CV event, third-plus CV events, post-third-plus CV events, and death. The transitions between the first, second & third-plus CV event states were explicitly estimated. Occupancy of the post-event states was modelled as a consistent 60 day period.

Clinical data	The relative efficacy of icosapent ethyl plus SOC and SOC for the economic analysis was estimated from the secondary prevention subgroup in the REDUCE-IT study. These data informed patient baseline characteristics, clinical variables, treatment duration, statin intensity, ezetimibe usage and AE rates for the economic analysis.
Extrapolation	To estimate long-term efficacy, the proportions of patients free from their first, second & third-plus CV events were extrapolated by fitting independent parametric curves to data from the REDUCE-IT study. The base case curves were selected by statistical fit, visual fit and clinical expert validation. For both treatment arms, exponential distributions were fitted to the proportions free from first CV event and log-logistic distributions fitted to the proportions free from second and third-plus CV events. The relative treatment effect was reduced by 1.5% to try to account for the possible detrimental effects of observed biomarker changes in the placebo arm of REDUCE-IT. CV mortality was modelled based on a proportions of events taking place within the first, second & third-plus event states being fatal. Those proportions were fixed across time, but differed across states and treatment arms. Non-CV mortality was modelled using all-cause general population mortality from the ONS Scottish national life tables, which was adjusted to exclude CV-related mortality. Those mortality rates were increased through hazard ratios from the Emerging Risk Factors Collaboration 2015[13] to account for prior CV events and diabetes status.
Quality of life	No health related quality of life data was collected as part of the REDUCE-IT study. The baseline utility value for the cohort was from Stevanović et al. 2016[14]. Utility values for specific CV events were estimated by applying utility multipliers to the baseline value. Those multipliers were taken from NICE guidelines.[15] Utility values for specific health states were estimated by accounting for the frequency and distribution of events in that state. Given the distribution of events differed across treatment arms, so did the utility values, albeit only slightly. Disutilities for AEs were sourced from the literature.
Costs and resource use	Medicine costs covered acquisition costs and AE costs. Icosapent ethyl and SOC are both administered orally, so no wastage or administration costs were included in the model, but the costs of a medical visit and a laboratory test for initiation of icosapent ethyl were included. Subsequent treatment costs were not included. Wider costs covered monitoring, follow-up and CV events. Terminal care costs for CV death were also included.
PAS	A PAS was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. The cost of generic statins were included in the model.

Results

This resubmission has been assessed under the fast track resubmission process.

The base case results are presented in Table 6.2. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the list price results can be presented.

The total costs for icosapent ethyl plus SOC were higher than those for SOC primarily due to the higher medicine acquisition costs. The quality-adjusted life years (QALY) gains associated with icosapent ethyl plus SOC were largely accrued in the no event health state.

Table 6.2. Base-case Results at list price

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SOC	12,377	10.467	7.405	-	-	-	-
Icosapent ethyl plus SOC	21,440	10.750	7.783	9,063	0.283	0.378	23,951

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years.

Sensitivity analyses

One-way sensitivity analysis indicated there was little sensitivity in the incremental cost-effectiveness ratio (ICER) to variation in most model parameters. The ICER was most sensitive to variation in the baseline utility value, used for the event-free health state.

In addition, the company conducted scenario analysis to explore areas of uncertainty. A selection of these scenarios are presented below in Table 6.3.

Table 6.3 Key scenario analyses results at list price

#	Scenario description	Base case description	ICER (£/QALY) List price
1	Treatment independent health state costs and utilities	Treatment dependent health state costs and utilities	20,756
2	40-year time horizon	36-year time horizon	22,465
3	Log-logistic distribution for proportion free from 1st event	Exponential distribution for proportion free from 1st event	26,276
4	Exponential distributions for proportions free from 2nd and 3rd-plus events	Log-logistic distributions for proportions free from 2nd and 3rd-plus events	26,306
5	Treatment effect waning over 5 years for those discontinuing after the study period	Treatment effect waning over 10 years for those discontinuing after the study period	27,481
6	Treatment effect waning over 10 years for those discontinuing during and after the study period		29,841
7	0.3% reduction in treatment effect due to uncertainty in the biomarker changes	1.5% reduction in treatment effect due to uncertainty in the biomarker changes	22,478
8	3% reduction in treatment effect due to uncertainty in the biomarker changes		26,028

9	Combined scenario: Exponential distributions for proportions free from 2nd and 3rd-plus events (Scenario 4) & Treatment effect waning over 5 years for those discontinuing after the trial period (Scenario 5)	29,929

Abbreviations: ICER, incremental cost-effectiveness;; QALY, quality-adjusted life year

*Other data were also assessed but remain confidential.**

Key strengths

The key strengths of the economic analysis were:

- The central comparator used in the economic evaluation was appropriate.
- The efficacy for the intervention and comparator was informed by a large randomised, double-blind phase III trial.
- There appeared to be little sensitivity in the cost-effectiveness results to variation in most model parameters.

Key uncertainties

The key uncertainties of the economic analysis were:

- The economic evaluation was heavily informed by the secondary prevention subgroup from the REDUCE-IT study and the generalisability of this to Scottish clinical practice was uncertain.
- The study was not designed for an analysis of the secondary prevention subgroup, as such the results for this subgroup were descriptive only and the effect size was uncertain.
- The company appeared to have followed good practice in selecting the parametric curves used to extrapolate the study data, however they remained a source of uncertainty. Using the same distribution type (exponential or log-logistic) for each survival curve reduced the cost-effectiveness of icosapent ethyl plus SOC compared with SOC (see Scenarios 3 & 4 in Table 6.3).
- The base case analysis included treatment waning, although this only applied to patients modelled as discontinuing treatment after the end of the study observation period. The company argued that the observed clinical data would already account for any loss in treatment effect in those who discontinued during the study. While some treatment loss may be captured for discontinuing patients within the clinical data, it was not clear that it would have been fully taken into account. An additional scenario applying treatment waning to all patients who discontinued led to a large increase in the ICER (see Scenario 6).
- The placebo used in the clinical study may have been associated with negative effects on clinical outcomes. The company sought to account for this by reducing the relative treatment effect by 1.5% in the base case, however, that remained a source of uncertainty. Alternative relative treatment reductions had a modest effect on the economic result (see Scenarios 7 & 8).

- Some patients may receive fibrates in clinical practice and the cost-effectiveness of icosapent ethyl compared with fibrates is unknown. The eligible number of patients expected to be receiving fibrates in Scotland was small.

Conclusion

After considering all the available evidence, the Committee accepted icosapent ethyl for restricted use in NHSScotland.

Guidelines and Protocols

The European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) published "2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk" in 2020.[5]

The Scottish Intercollegiate Guidelines Network (SIGN) published "Risk estimation and the prevention of cardiovascular disease: a national clinical guideline" (SIGN 149) in 2017.[2]

The National Institute for Health and Care Excellence (NICE) published the "Cardiovascular disease: risk assessment and reduction, including lipid modification" clinical guideline in 2014, which was updated in 2016.[15]

Additional Information

Product availability date

31 December 2021

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Icosapent ethyl	Two 998mg capsules orally twice daily	1,750

Costs from BNF online on 06/02/23. Costs do not take any patient access schemes into consideration.

Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 75,565 patients eligible for treatment with icosapent ethyl in year 1, rising to 75,891 patients in year 5 to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 26 May 2023.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.