# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Appraisal consultation document

# Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using icosapent ethyl in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

**This document has been prepared for consultation with the consultees.** It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?



Issue date: January 2022

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using icosapent ethyl in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: Tuesday 22 February 2022

Second appraisal committee meeting: To be confirmed

Details of membership of the appraisal committee are given in section 3.

# 1 Recommendations

1.1 Icosapent ethyl is not recommended, within its marketing authorisation, for reducing the risk of cardiovascular events in adults who:

- have a high cardiovascular risk with raised triglycerides (150 mg/dL [1.7 mmol/litre] or more) and
- are having statins and
- have established cardiovascular disease, or
- diabetes and at least 1 other cardiovascular risk factor.

1.2 This recommendation is not intended to affect treatment with icosapent ethyl that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

**Why the committee made these recommendations**

There are currently no treatment options to reduce the risk of cardiovascular events in people taking statins who have raised triglycerides.

Clinical trial evidence suggests that icosapent ethyl reduces the risk of cardiovascular events in people who have established cardiovascular disease (secondary prevention). The evidence on its use by people without established cardiovascular disease but who have diabetes and at least 1 cardiovascular risk factor (primary prevention) is less clear. It is also uncertain how well icosapent ethyl works because it was compared with a placebo that may itself increase cardiovascular risk. Also, the trial may not be generalisable to the NHS.

The cost-effectiveness estimates for icosapent ethyl are uncertain. This is because there are several concerns with the company's economic model, including its structure, how treatment effect was modelled and what happens when people stop having treatment.

Further information and analyses are needed to address the uncertainties. So, icosapent ethyl is not recommended.

# 2 Information about icosapent ethyl

## Marketing authorisation indication

2.1 Icosapent ethyl (Vazkepa, Amarin Corporation) is indicated 'to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥150 mg/dL [1.7mmol/l]) and established cardiovascular disease or diabetes, and at least one other cardiovascular risk factor'.

## Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

## Price

2.3 Icosapent ethyl costs £173 per pack of 120 capsules (including VAT; company submission). Costs may vary in different settings because of negotiated procurement discounts.

# 3 Committee discussion

The appraisal committee considered evidence submitted by Amarin Corporation, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

## Treatment pathway and comparator

### People with elevated triglycerides who are having statins with or without ezetimibe would welcome a treatment option

3.1 NHS England estimate that between 25% and 35% of people having statin therapy have elevated triglycerides. The patient and clinical experts explained there is an unmet need for this population. This is because

there are no pharmaceutical treatments for people at risk of cardiovascular events who have elevated triglycerides despite having statins with or without ezetimibe. They explained the aim of treatment would be to reduce the risk of cardiovascular events. The patient expert commented that lifestyle changes, including diet and exercise can be helpful at reducing risk of cardiovascular events. The patient expert noted the importance of treatment options because current ways of reducing cardiovascular risk may not work for everyone. The committee concluded that people with elevated triglycerides who are having statins with or without ezetimibe would welcome a treatment option.

## Statins with or without ezetimibe is an appropriate comparator

3.2 The marketing authorisation for icosapent ethyl says it should be used in addition to statin therapy. The company submission, which was based on the REDUCE-IT trial (see section 3.6), also noted people could have ezetimibe in addition to statins. The clinical experts said that fibrates are not used to reduce the risk of cardiovascular events in people with moderately elevated triglycerides. They explained that fibrates are used by people with very high triglycerides to prevent pancreatitis, which is a different indication. The clinical experts confirmed that there are no treatments to reduce cardiovascular risk for people with elevated triglycerides who have statins with or without ezetimibe. Therefore, the committee agreed statins with or without ezetimibe was the appropriate comparator.

## Icosapent ethyl is likely to be used mostly in a primary care setting

3.3 The company noted it expected icosapent ethyl to be used in a primary care setting. The clinical experts commented that icosapent ethyl would be used in both primary and secondary care settings but it would likely be used more in primary care. The committee concluded icosapent ethyl would likely be used mostly in a primary care setting.

## Population

### The population in the company's submission is narrower than the marketing authorisation in terms of LDL-C levels and is acceptable

3.4 Icosapent ethyl's marketing authorisation does not specify age or LDL-C thresholds (see section 2.1). However, the company only provided evidence for icosapent ethyl from the REDUCE-IT trial. This included people aged 45 and over who had cardiovascular disease, and people aged 50 and over who had diabetes and at least 1 other cardiovascular risk factor (see section 3.5). The trial also only included people with LDL-C levels above 1.04 mmol/litre and less than or equal to 2.60 mmol/litre. A clinical expert noted that there are people younger than 45 who have cardiovascular disease and elevated triglycerides in the NHS. They explained that many of these people have South Asian family backgrounds. The ERG commented that the treatment effect for icosapent ethyl varies by age, with a larger benefit observed in people under 65 (hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.56 to 0.75) than in people aged 65 or older (HR 0.87, 95%CI 0.76 to 1.00). The committee was aware that restricting by age may result in an equalities issue and would consider this in its decision making (see section 3.18). The committee concluded the company's submission for icosapent ethyl was narrower than the marketing authorisation and it was acceptable to use the LDL-C thresholds from REDUCE-IT.

### It is appropriate to consider the effects of icosapent ethyl separately for the primary and secondary prevention subgroups

3.5 The company provided evidence for 2 separate risk groups from the REDUCE-IT trial: primary and secondary prevention. The primary prevention group included people aged 50 and over with type 1 or 2 diabetes and at least 1 additional cardiovascular risk factor. The risk factors included being aged 55 or over, cigarette smoking, hypertension, high-density lipoprotein cholesterol levels below 1.04 mmol/litre, high-

sensitivity C-reactive protein above 3.0 mg/litre, renal dysfunction, retinopathy, micro- or macroalbuminuria, or ankle-brachial index below 0.9. People in the secondary prevention group were aged 45 years and over with established cardiovascular disease. The committee noted these subgroups were clinically distinct and concluded it was appropriate to consider the effects of icosapent ethyl separately for primary and secondary prevention.

## Clinical evidence

### The generalisability of the results from REDUCE-IT to the NHS in England is uncertain

3.6 The company provided clinical evidence from REDUCE-IT, a randomised trial comparing icosapent ethyl with a mineral oil placebo. The trial included people in primary and secondary prevention groups (see section 3.5). The trial included people who had statins with or without ezetimibe, triglyceride levels of above 1.53 mmol/litre and below 5.64 mmol/litre, and LDL-C levels of 1.04 mmol/litre to 2.60 mmol/litre. In the trial, 8,179 people were randomised and 29% were in the primary prevention group and 71% were in the secondary prevention group. The primary endpoint was time from randomisation to the first occurrence of any component of the major adverse cardiovascular event (MACE) composite outcome, which included: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularisation or unstable angina. The ERG noted that REDUCE-IT did not include any people from the UK, which increases uncertainty around the generalisability of the results to the NHS in England. A clinical expert commented that the trial did not represent the ethnic diversity in England. They noted that people with South Asian family backgrounds may benefit more from icosapent ethyl. The company compared the baseline characteristics of the primary and secondary prevention subgroups with similar populations from Steen et al. 2016. This was a retrospective study of 183,565 people with or without atherosclerotic cardiovascular disease

from The Health Improvement Network database in the UK. The company noted that age, gender, BMI and systolic blood pressure were similar between REDUCE-IT and Steen et al. The exact values from REDUCE-IT are considered confidential by the company and cannot be reported here. However, the ERG noted that there were substantial differences between REDUCE-IT and Steen et al. that might modify treatment effect. It also questioned the relevance of Steen et al. because the study is 5 years old. The clinical adviser to NHS England raised additional concerns about REDUCE-IT's generalisability based on the current management of high-risk cardiovascular disease and diabetes. They noted that several treatments available in the NHS were used by only a small proportion of people in REDUCE-IT or not at all. The adviser noted inclisiran, which is recommended by NICE for treating primary hypercholesterolaemia or mixed dyslipidaemia as an adjunct to diet in adults, was not a permitted concomitant treatment in REDUCE-IT. Therefore, the effect of icosapent ethyl on reducing the risk of cardiovascular disease in people who have inclisiran is unknown. The clinical adviser also commented that standard care in the NHS for diabetes includes SGLT2 inhibitors but it is uncertain how many people in REDUCE-IT had these treatments. They explained that the treatment landscape for high-risk cardiovascular disease and type 2 diabetes in the NHS in England makes the generalisability of REDUCE-IT uncertain. The committee concluded that the generalisability of the results from REDUCE-IT to the NHS in England was uncertain.

## Icosapent ethyl's mechanism of action is not fully understood, which adds uncertainty

3.7 The company stated that icosapent ethyl's mechanism of action is not fully understood. The company noted it appears to modulate the atherosclerosis pathway by lipid and non-lipid effects. It explained the primary lipid effect is reducing triglyceride levels. It added that the non-lipid effects may include localised anti-inflammatory effects, regulation of lipid metabolism gene transcription, antithrombotic effects and plaque reduction. The clinical experts also commented that the mechanism of

action is uncertain. They explained that the reduction in cardiovascular risk observed in REDUCE-IT was larger than what would be expected from a reduction in triglycerides alone. The committee concluded that the mechanism of action is not fully understood, which adds uncertainty to the trial's results.

## The treatment effect of icosapent ethyl is uncertain because of the mineral oil placebo in REDUCE-IT

3.8 The placebo group in REDUCE-IT had 4 g of light mineral oil per day. In the intention to treat population, icosapent ethyl significantly reduced the risk of a composite MACE outcome compared with placebo (HR 0.75, 95% CI 0.68 to 0.83). Icosapent ethyl significantly reduced the first occurrence of the MACE outcome in the secondary prevention subgroup compared with placebo (HR 0.73, 95% CI, 0.65 to 0.81). A similar trend was reported for the primary prevention subgroup, although it was not statistically significant (HR 0.88, 95% CI, 0.70 to 1.10). A professional group and the NHS England clinical adviser expressed concerns about the REDUCE-IT results, in part because of the use of mineral oil. They commented that mineral oil was not a true neutral oil and may have increased the risk of a cardiovascular event in the placebo group. This would exaggerate the observed difference in cardiovascular events between the icosapent ethyl and placebo groups. The professional group and NHS England clinical adviser also commented that results of a similar trial, STRENGTH, did not show the same magnitude of benefit as REDUCE-IT. STRENGTH compared a combination of eicosapentaenoic acid and docosahexaenoic acid, which is similar to icosapent ethyl, with a corn oil placebo. The NHS England clinical adviser explained they expected to see analyses where the magnitude of treatment effect was reduced by 7% to account for the estimated negative effect of mineral oil. The committee noted that this should be done by re-estimating the relative effects by adjusting the placebo group. The ERG explained that the Takahito et al. 2021 paper comparing REDUCE-IT with STRENGTH suggested the differences in results might be partially explained by

differences in placebo comparators. But it cautioned that there were other possible explanations, including that corn oil could decrease the risk of MACE or that there were underlying differences in patient characteristics between the trials. The ERG highlighted a systematic review by Olshansky et al. 2020 that concluded mineral oil at the quantities used as placebos likely does not significantly affect study conclusions. However, the ERG noted the systematic review had some limitations and one of the co-authors was employed by Amarin. The committee noted that the effect of icosapent ethyl is uncertain because of the mineral oil placebo. The committee was aware that the European Medicines Agency reported analyses by the company suggesting the putative negative effect of mineral oil should not account for more than 3% of MACE events. The committee also noted the Takahito et al. paper commented there was an unexplained additional 13% benefit in REDUCE-IT. It concluded it would like to see scenarios where the magnitude of the treatment effect was reduced by 7% and 13%.

## Icosapent ethyl has manageable adverse events

3.9 In REDUCE-IT, similar proportions of people having icosapent ethyl (81.8%) and placebo (81.3%) reported adverse events. The most commonly reported adverse events among people having icosapent ethyl were diarrhoea (9.0%), back pain (8.2%) and hypertension (7.8%). The company noted that diarrhoea occurred statistically more frequently among people who had placebo (11.1%) than icosapent ethyl (9.0%). The clinical experts noted icosapent ethyl appears to be generally well tolerated. But they had some concerns around specific adverse events. In REDUCE-IT, there were significant differences in the incidence of atrial fibrillation (5.3% icosapent ethyl, 3.9% placebo), bleeding-related events (11.8% icosapent ethyl, 9.9% placebo), constipation (5.4% icosapent ethyl, 3.6% placebo) and peripheral oedema (6.5% icosapent ethyl, 5.0% placebo). The committee noted that some fish oil products can be associated with unpleasant burps that may affect adherence. The

company explained that reports of burps related to icosapent ethyl were relatively low, although it did not have an exact figure. The committee would have preferred to see the proportions of people experiencing burps in each treatment group. The committee noted the concerns about some adverse events, but concluded icosapent ethyl was generally well tolerated with manageable adverse events.

## The economic model

### The results from the company's model are uncertain and more information is needed

3.10 The company's model included 8 health states: cardiovascular event free, first event, post-first event, second event, post-second event, third or more event, post-third or more event, and death. The events in the model were based on the composite 5-point MACE outcome from REDUCE-IT (see section 3.6). The health states were populated by fitting parametric models to the Kaplan–Meier curves for first, second and third plus cardiovascular events from REDUCE-IT following a partitioned survival approach. The model used a 1-day cycle length and a lifetime horizon, equivalent to 36 years. The company used baseline utility values from the literature (Stevanovic et al. 2016 and O'Reilly et al. 2011) and health state multipliers from NICE's guideline on cardiovascular disease: risk assessment and reduction, including lipid modification. The ERG noted several concerns with the model structure and differences from models for similar appraisals, including that it used a partitioned survival type approach to estimate the probability of having a cardiovascular event. The ERG was concerned that the model structure assumed independence of endpoints, meaning the probability of having a second or third cardiovascular event was independent of the time of the previous events. It commented the company's model did not explicitly model nonfatal cardiovascular events, it used a 1-day cycle length, and there was uncertainty in the time to event analysis (see section 3.12). The

committee noted that it had not seen evidence that the company's model could predict the survival from REDUCE-IT. The committee commented that it was unusual that the company's entire model was based on REDUCE-IT, rather than applying the relative treatment effect observed in the trial to a baseline risk estimated using routine datasets. The committee concluded that the results of the company's model were uncertain because of the model structure and more information was needed before it can be used for decision making.

## Using the composite 5-point MACE outcome in the model increases uncertainty

3.11 The company's model used the same composite MACE outcome as REDUCE-IT (see section 3.6). The ERG was concerned that the composite outcome could mask the treatment effect in relation to individual cardiovascular events. The ERG highlighted that the hazard ratios for cardiovascular death in the intention to treat population (HR 0.80, 95% CI 0.66 to 0.98) and death from any cause (HR 0.87, 95% CI 0.0.74 to 1.02) were larger than that for the composite 5-point MACE (HR 0.75, 95% CI 0.68 to 0.83). The ERG noted it would like to see smoothed empirical hazard plots for each individual event included in the MACE outcome. The company noted that although the composite outcome was used, the distribution of specific cardiovascular events was applied in the model. The company explained that the effect of icosapent ethyl on each specific event occurring as a first, second or third plus event was taken into account. However, the ERG commented that applying direct estimates of time to each event is not necessarily equivalent to the combination of time to the composite and proportion of the composite attributed to each event. The clinical experts commented that the composite MACE outcome is common for large clinical trials but one expert said that there was some debate about if all components of the MACE should be used. The committee was concerned that the composite outcome might be double counting risk. It noted that revascularisations

accounted for a large proportion of second and third events (the exact values are considered confidential by the company and cannot be reported here). It noted that coronary revascularisation could be an indicated procedure based on a preceding event, such as myocardial infarction. The committee concluded the composite 5-point MACE outcome increases uncertainty and it would like to see the Kaplan–Meier curves and hazard ratios for each of the individual cardiovascular events.

## Additional information and analyses are needed for the company's updated time to event modelling

3.12 The company originally fitted separate parametric models to the icosapent ethyl and placebo arms for first, second and third plus events in REDUCE-IT. The ERG noted the company had not followed the Decision Support Unit's technical support document 14. Specifically, the company used independent survival models without considering proportional hazards. The ERG also highlighted that the company had not provided the full time to event analysis, including fitted models and justification for selection, at technical engagement. In response, the company updated its time to event analysis. It tested the proportional hazards assumption and fitted 1 parametric model to the full Kaplan–Meier curve for each composite event, with treatment group as a covariate, following technical support document 14. The company also provided the updated models and the statistical fit for each. Because the company's updated time to event analysis was submitted after technical engagement, the ERG did not have enough time to fully validate it before the committee meeting. The ERG did highlight that the model allowed different curves to be selected for each treatment group, suggesting that it was not a jointly modelled approach. The committee agreed that the company should explain this and why the Weibull curve could not be fitted. It noted that it could be reasonable to fit independent models to each treatment group without using a hazard ratio even if the proportional hazards assumption was met. The ERG noted that the time to event analysis was only

provided for the intention to treat population and not for the primary and secondary prevention subgroups. It also noted that different parametric curves might be more suitable for the subgroup analyses. The committee noted that the company should also provide internal and external validation of the subgroup extrapolated curves. This should include a comparison of model-predicted overall survival compared with overall survival in REDUCE-IT. This should also consider clinical expert judgements on the plausibility of the long-term model predictions of having 0, 1, 2 or 3 plus events, and overall survival. The committee concluded the company need to provide additional information and analyses for its updated time to event modelling to allow this to be fully critiqued before it could be considered suitable for decision making.

### The modelling of treatment waning and time to treatment discontinuation are not appropriate

3.13 The company's base case assumed that the treatment effect for icosapent ethyl continued at the same level for the duration of the model with no treatment waning. The company commented that similar recent appraisals did not include treatment waning, including the appraisals of inclisiran (TA733), evolocumab (TA394) and alirocumab (TA393). The company provided an analysis of treatment effect over time, which showed the treatment effect did not decrease during the follow up period (the exact values are considered confidential by the company and cannot be reported here). The ERG noted that the confidence interval for the primary prevention subgroup crossed 1 in the follow-up period. The ERG also noted that the clinical trial was shorter than the modelled time horizon, so there is unresolvable uncertainty about the long-term treatment benefits. The ERG's preferred assumption was to include a 10-year post-trial treatment waning effect for all events. The clinical expert commented that given the absence of long-term data it is difficult to determine the appropriateness of a treatment waning assumption. However, the expert noted that related treatments for cardiovascular disease, such as statins,

have long-term effects. The expert commented that the company's assumption of no treatment waning was likely reasonable. The committee noted that in the recent related appraisal of bempedoic acid and ezetimibe (TA694), the company's model assumed results achieved at 12 weeks were maintained for the duration of the model's time horizon, or until treatment was stopped. It was concerned that treatment discontinuation was not linked to treatment effect in the icosapent ethyl model. It would have liked to see the full analysis for time to treatment discontinuation, including for subgroups. The committee concluded it would have preferred a method linking treatment effect and discontinuation by changing the hazard ratio to 1 at an appropriate time after people stopped icosapent ethyl.

### Non-cardiovascular-related deaths hazard ratios are uncertain

3.14 The company's model included mortality for cardiovascular-related death and non-cardiovascular-related death. The model used non-cardiovascular-related death hazard ratios for icosapent ethyl and the placebo groups separately. The ERG commented that it was not clear why non-cardiovascular death should be treatment dependent because cardiovascular death is already captured in the model. It preferred to apply a weighted average of the hazard ratios for non-cardiovascular-related death by health state to both treatment groups. The company disagreed with the ERG's method because the averages were calculated for the intention to treat population and did not account for the proportion of people in the primary versus secondary prevention subgroups. The company elaborated that people in the two subgroups are not comparable. It added that diabetes and number of prior events were non-cardiovascular-related death modifiers. The committee concluded the non-cardiovascular-related death hazard ratios are uncertain and it would like to see evidence that diabetes and number of previous events are non-cardiovascular-related death modifiers.

### The company's model has uncertainties that should be addressed before it is compared with the validation model

3.15 Due to the ERG's concerns with the company's model, the company provided a microsimulation model for validation. The validation model was originally developed for the US setting but was adapted to a UK NHS setting by using the same costs, utilities and background mortality as the company's model. The validation model also used cardiovascular event data from REDUCE-IT. The company provided a comparison of its model with the validation model. The validation model explicitly modelled individual nonfatal cardiovascular events, had a cycle length of 6 months and assumed people experienced an acute utility for 18 months following an event, after which they experienced a post-event utility. The company also provided a 30-year comparison of the expected number of first, second and third events, people discontinuing icosapent ethyl, and people alive in the company's and validation models. It noted the models produced similar clinical estimates. The ERG noted that additional details on the discrepancies in the original cross validation and explanation for the remaining differences in the updated cross validation would be helpful. The committee concluded that there were unresolved uncertainties in the company's model that should be addressed before comparison with the validation model.

## Cost-effectiveness estimates

### Because of the uncertainty an acceptable ICER is around £20,000 per QALY gained

3.16 NICE's guide to the methods of technology appraisal notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee

will be more cautious about recommending a technology if it is less certain about the ICERs presented.

The committee noted the high level of uncertainty, specifically:

- the generalisability of the clinical trial results to the NHS in England (see section 3.6)
- the robustness of the clinical-effectiveness results because of the mineral oil placebo (see section 3.8)
- the differences in results from the REDUCE-IT and STRENGTH trials (see section 3.8)
- the appropriateness of the company's model (see section 3.10)
- the composite 5-point MACE outcome in the model (see section 3.11)
- how treatment waning and time to treatment discontinuation were modelled (see section 3.13).

Therefore, it agreed that an acceptable ICER would be around £20,000 per QALY gained. The committee noted that additional analyses and information were needed for decision making. The committee would have preferred:

- scenarios in which the treatment benefit of icosapent ethyl from REDUCE-IT is reduced by 7% and 13% (see section 3.8)
- the Kaplan–Meier curves, hazard ratios and empirical hazard plots for each individual event from the composite MACE outcome (see section 3.11)
- a comparison of model-predicted overall survival compared with overall survival in REDUCE-IT (see section 3.12)
- full time to event analysis, following technical support document 14, for the primary and secondary prevention subgroups, including clarity on the updated time to event analyses, consideration of clinical expert judgements on the plausibility of the long-term model predictions of having 0, 1, 2 or 3 plus events and overall survival (see section 3.12)

- full analysis for time to treatment discontinuation, including for subgroups (see section 3.13)
- treatment effect and discontinuation linked so that when people stop icosapent ethyl, the hazard ratio changes to 1 at an appropriate time, including scenarios for all 6 potential models for time to treatment discontinuation (see section 3.13)
- further evidence that diabetes and number of prior events are non-cardiovascular-related death modifiers (see section 3.14)
- detail on the discrepancies in the original cross validation and explanation for the remaining discrepancies in the updated cross validation (see section 3.15).

## Icosapent ethyl is not cost effective for reducing the risk of cardiovascular events

3.17 The company's base case included the updated time to event analysis, assumed no treatment waning for icosapent ethyl, and used the exponential curve to extrapolate time to treatment discontinuation. The company's base case results for icosapent ethyl compared with a stable dose of statins with or without ezetimibe were:

- £28,266 per QALY gained for the intention to treat population
- £22,796 per QALY gained for the secondary prevention subgroup
- £85,438 per QALY gained for the primary prevention subgroup.

Because the company's base case was based on time to event analysis submitted after technical engagement, the ERG did not have sufficient time to update its base case. In its previous base case, the ERG's cost-effectiveness estimates were much higher than the company's and above the threshold NICE normally considers a cost-effective use of NHS resources. The committee noted the uncertainty with the economic model and the additional information that was needed to inform decision making. It noted that due to the additional analyses and information needed from the company that it did not have a committee-preferred ICER. However,

the committee noted that the company's own ICER for the primary prevention subgroup was much higher than what NICE normally considers an acceptable use of NHS resources. It therefore concluded that the primary prevention subgroup was very unlikely to be cost effective in any additional analyses. It also recalled that it was appropriate to consider each clinically distinct subgroup separately (see section 3.5). Therefore, it would be appropriate for the company to only provide additional analyses and information for the secondary prevention subgroup. The committee concluded that given the uncertainty and the company's base case ICERs, icosapent ethyl could not be recommended for any of the populations considered.

## Other factors

### The committee considered potential equality issues in its decision making

3.18 A patient organisation and clinical expert raised several potential equalities issues. They noted that people with Black, Asian and minority ethnic family backgrounds are more likely to have elevated triglycerides. The patient organisation also commented that people living in England's most deprived areas are almost 4 times more likely to die prematurely from cardiovascular disease than those in the least deprived. It also explained that compared with the general population, people with severe mental illness are more likely to develop and die from preventable conditions, including cardiovascular disease. It also noted that people with learning disabilities are at increased risk of developing cardiovascular disease. The clinical expert noted that some religions have restrictions on fish products. The committee considered these to be important issues. The committee concluded that its recommendation for icosapent ethyl would apply to all patients and that the recommendation would not affect people protected by the equality legislation any differently.

### End of life criteria do not apply

3.19 NICE's advice about life-extending treatments for people with a short life expectancy did not apply.

### The committee has not seen evidence of additional benefits that are not captured in the cost-effectiveness analysis

3.20 The clinical experts noted that icosapent ethyl may be considered innovative because it appears to work on a disease pathway that is not fully understood. The committee concluded that it had not seen evidence of additional gains in health-related quality of life associated with icosapent ethyl over those already included in the QALY calculations.

## Conclusion

### Icosapent ethyl is not recommended for reducing the risk of cardiovascular events in people with elevated triglycerides

3.21 The committee noted uncertainty in the clinical effectiveness evidence for icosapent ethyl because of the mineral oil placebo (see section 3.8). It also noted concerns about the generalisability of the trial results to the NHS in England (see section 3.6). It was concerned about the company's modelling approach (see section 3.10), including how the treatment effect after discontinuation was modelled (see section 3.13) and the composite outcome (see section 3.11). The committee noted that the company's updated time to event analysis had not been fully validated by the ERG and requested additional information and analyses. It noted the company's base case results were all above £20,000 per QALY gained. Therefore, the committee concluded that icosapent ethyl is not recommended for reducing the risk of cardiovascular events in people with elevated triglycerides.

# 4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Stephen O'Brien
Chair, appraisal committee
January 2022

# 5 Appraisal committee members and NICE project team

## Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

## NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Catie Parker**

Technical lead

**Alex Filby**

Technical adviser

**Louise Jafferally**

Project manager

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