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, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: March 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: 19 April 2022

Third appraisal committee meeting: 4 May 2022

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 (mineral oil) 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. The cost-effectiveness estimates are also likely to be higher than

what NICE normally considers an acceptable use of NHS resources. 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 estimated 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 the 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 might be used in secondary care 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 older who had cardiovascular disease, and people aged 50 and older 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 3.2020). 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 for the secondary prevention subgroup

3.5 In its original submission, 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 older with type 1 or 2 diabetes and at least 1 additional cardiovascular risk factor. The risk factors included being aged 55 or older, cigarette smoking, hypertension, HDL-C 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 older with established cardiovascular disease. The committee noted these subgroups were clinically distinct. In response to consultation, the company provided analyses that focused only on the secondary prevention subgroup. The committee noted this was consistent with its discussions from the first meeting. It noted that icosapent ethyl was unlikely to be cost effective in the primary prevention subgroup, because the cost-effectiveness estimates were substantially higher than the range normally considered an acceptable use of NHS resources. It concluded it was appropriate to focus on the effects of icosapent ethyl for the secondary prevention subgroup.

Clinical evidence

The population in REDUCE-IT may not be generalisable to the NHS in England

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 subgroups (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. This included cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularisation and 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, sex, 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. In response to consultation, the company reiterated the similarities between the REDUCE-IT and Steen et al. secondary prevention populations in terms of BMI and systolic blood pressure. The company also noted 2 observational studies from France and Canada that showed similar residual cardiovascular risk as REDUCE-IT. The ERG commented that these studies did not provide evidence for the NHS in England. The company also highlighted ethnic similarities between the populations in England and REDUCE-IT. The company further explained that there was no interaction for icosapent ethyl reducing the risk of cardiovascular events according to ethnicity in REDUCE-IT ('white' HR 0.77, 95% CI 0.69 to 0.85 and 'non-white' HR 0.60, 95% CI 0.43 to 0.83). The committee noted that there were differences between REDUCE-IT and Steen et al. in terms of the proportion of people that had recent acute coronary syndrome, diabetes, hypertension and ischaemic stroke. It concluded that the population from REDUCE-IT may not fully represent people in the NHS in England, which increases uncertainty around the generalisability of the results to the NHS in England.

Current management of cardiovascular disease and diabetes is not fully reflected in REDUCE-IT

3.7 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. In response to consultation, the company provided the proportion of people in REDUCE-IT who were having SGLT2 inhibitors or GLP-1 agonists. The values are considered confidential by the company and cannot be reported here. The company acknowledged that the use of PCSK9 inhibitors was an exclusion criterion in REDUCE-IT. But it noted a recent cross-sectional European study found that only 1.1% of patients with established atherosclerotic cardiovascular disease used PCSK9 inhibitors. The committee concluded that the current management of cardiovascular disease and diabetes is not fully reflected in REDUCE-IT, so the generalisability of the trial results is uncertain.

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

3.8 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. In response to consultation, the company stated the mechanism of action is likely multifactorial and that it can positively alter the development, progression and stabilisation of atherosclerotic plaque. The company also noted that other related technologies that have been appraised by NICE, such as SGLT2 inhibitors, have uncertain mechanisms of action. The committee concluded that the mechanism of action for icosapent ethyl 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

3.9 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 may not be a true neutral oil and may have increased the risk of cardiovascular events 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 ERG explained that the Doi 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. In response to consultation, the company commented that some parameters associated with cardiovascular risk increased in the placebo group of REDUCE-IT. However, it stated that it was uncertain if these changes were because of the natural history of the disease, variability or regression to the mean, or negative effects of mineral oil. The company provided a comparison of cardiovascular outcomes trials from 2003 to 2019. The comparison found that 79% of studies reported increases in LDL-C after statin stabilisation, similar to what was observed in the placebo group of REDUCE-IT. The experts explained that among cardiovascular disease researchers and clinicians, there is an ongoing debate about mineral oil placebos and the impact on trial outcomes. The committee concluded that the relative effect of icosapent ethyl was uncertain because of the mineral oil placebo.

It is appropriate to consider scenarios for an estimated reduction in treatment effect from 3% to 10%

3.10 At the first meeting, the NHS England clinical adviser explained they expected to see analyses with the magnitude of treatment effect reduced by 7% to account for the estimated negative effect of mineral oil. The committee noted that this should be done by adjusting the placebo group to re-estimate the relative effects. The committee was aware that the

company provided analyses to the European Medicines Agency based on the 3-point MACE assuming that the potential negative effect of mineral oil on MACE events was between 0.3% and 3%. The committee also noted the Doi et al. 2021 paper commented there was an unexplained additional 13% benefit in REDUCE-IT. At the first meeting, the committee requested scenarios with the magnitude of the treatment effect reduced by 7% and 13%. In response to consultation, the company provided scenarios with the clinical effectiveness of icosapent ethyl reduced by 0.3%, 1%, 2% or 3% based on the analyses provided to the European Medicines Agency. The company explained that the range of 7% to 13% was not plausible because it was based on a single Danish observational study. The ERG provided scenarios with the clinical effectiveness reduced by 7% and 13%. A clinical expert commented that it was difficult to quantify the potential negative effects of mineral oil and there was significant uncertainty. As such, they could not state whether the 7% or 13% scenario was more plausible. The committee recalled that the experts also explained there is an ongoing debate about mineral oil placebos and the impact on trial outcomes. The committee was aware that the European public assessment report on icosapent ethyl notes that a higher value than the company's assumptions about the negative effect of mineral oil may be more realistic, but that it would not be more than 10%. Considering the ongoing debate in the clinical community about mineral oil placebos, and the range of reductions in treatment effect reported in the literature, the committee concluded it would be appropriate to consider scenarios estimating a reduction in treatment effect from 3% to 10%, based on the discussion in the EPAR. The committee considered the scenario using around 7% in its preferred analysis because it was near the middle of the range and aligned with Doi et al.

Icosapent ethyl has manageable adverse events

3.11 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 (icosapent ethyl is derived from fish oil). At its first meeting, the committee requested the proportions of people experiencing burps in each treatment group. In response to consultation, the company provided the proportions of people who experienced burps and discontinued treatment for this reason in the icosapent ethyl and placebo groups (the values are considered confidential by the company and cannot be reported here). The company noted that unpleasant burps had very little impact on treatment adherence. 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

3.12 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 using 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 in similar appraisals. In recent hypercholesterolaemia and mixed dyslipidaemia appraisals, the economic models have often followed a Markov approach and used specific cardiovascular event types as health states. The ERG noted that the company's partitioned survival approach to estimate the probability of having a cardiovascular event deviated from the modelling approach in related NICE appraisals. 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 and used a 1-day cycle length. 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. In response to consultation, the company explained that its model was designed to align with REDUCE-IT, in which people progressed through health states in a specific order. It also commented that time from randomisation to a first, second or third plus event was used so there were no issues with crossover of events during the trial period. Beyond the trial period, the company noted that any extrapolation curves that crossed were considered clinically implausible and disregarded. The ERG noted that these comments were not justification for the model structure and uncertainty remains. The company also provided a comparison of the model estimated survival and mortality from REDUCE-IT. The committee noted the model appeared to overestimate mortality in both the placebo and icosapent ethyl groups in

the 5-year comparison. The committee concluded that the results of the company's model were uncertain because of the model structure and the discrepancy between model and trial outcomes.

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

3.13 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 0.74 to 1.02) were larger than that for the composite 5-point MACE (HR 0.75, 95% CI 0.68 to 0.83). The 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 most 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. At its first meeting, the committee requested Kaplan–Meier curves and hazard ratios for each of the individual cardiovascular events. In response to consultation the company provided Kaplan–Meier curves and hazard ratios over time for each individual event type in the

composite outcome. The ERG commented that in the Kaplan–Meier curves for cardiovascular death, nonfatal myocardial infarction and nonfatal stroke, there appeared to be a lag in the icosapent ethyl and placebo curve separation of around 1 to 2 years. The ERG explained that the lag in curve separation for these key outcomes might mean the composite outcome biases the treatment effect in favour of icosapent ethyl in the first 1 to 2 years of treatment. The ERG also commented that when considering the hazard ratios over time, there are some differences in pattern between the individual event types and the composite. The committee welcomed the additional information from the company but concluded that using the composite outcome in the model increased uncertainty.

The updated time to event modelling is acceptable

3.14 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 or provided the full time to event analysis at technical engagement. In response, the company updated its time to event analysis. 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. The committee noted that the company should also provide internal and external validation of the subgroup extrapolated curves. 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. At the first meeting, the committee requested this additional information and analyses for the time to event modelling. In response to consultation, the company provided updated time to event analysis for the secondary prevention subgroup. The company selected the curve with the best statistical fit. For the first event that was the exponential distribution and for both the second and third plus event curves, it selected the log-logistic. The ERG agreed with the company that there was some uncertainty around the most appropriate

extrapolation for the second and third plus event curves, but that this has a minor impact on the cost-effectiveness results. The ERG commented that the time to event analysis appeared appropriate. The committee concluded that the updated time to event analysis was acceptable.

It is plausible that the treatment effect may be lost after 10 years if treatment is discontinued

3.15 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 effect waning. The company commented that similar recent appraisals did not include treatment effect 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 clinical expert commented that given the absence of long-term data it is difficult to determine the appropriateness of a treatment effect 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 effect waning was likely reasonable. However, the committee was concerned that treatment discontinuation was not linked to treatment effect in the icosapent ethyl model. At its first meeting, the committee noted 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. In response to consultation, the company commented that the clinical efficacy curves accounted for efficacy lost because of discontinuation because they are based on the intention to treat population, which includes all patients in the icosapent ethyl trial, regardless of treatment discontinuation. The committee acknowledged this, but considered that if the proportion of patients continuing treatment reduced over the model time horizon, it would expect the average treatment effect to be lower than that captured in the trial.

The company's base case did not apply a treatment waning effect. However, it did provide 2 scenarios assuming that once a person discontinued treatment, after a period of either 10 or 20 years, they would have equivalent clinical outcomes to people in the placebo group. The company explained that because of the model structure, when assuming that people who discontinue treatment follow the efficacy of the placebo group, it was assuming that all events that were avoided occur on discontinuation which was not clinically plausible. The ERG noted that the company did not provide the proportion of modelled people who would experience multiple events, so it is uncertain how impactful this is. The ERG noted that when comparing across appraisals, it is important to consider discontinuation rates and treatment effects in those settings. The committee considered the issue of treatment effect waning in previous related appraisals and noted that in previous appraisals, treatment effect was linked to treatment continuation. It recalled that at its first meeting, it 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 recognised that in NICE's appraisal of alirocumab, the company had assumed 100% treatment continuation and compliance over the entire time horizon. The committee noted that this assumption likely would not be appropriate in this appraisal because a significant proportion of people discontinued treatment by the end of follow-up in REDUCE-IT (the value is considered confidential by the company and cannot be reported here). The committee noted the assumptions of complete continuation and no treatment effect waning were also used in the appraisal of inclisiran. The committee commented that the icosapent ethyl appraisal had different considerations. It noted that there was uncertainty around the assumption that the treatment effect observed over the REDUCE-IT trial period would continue for the entire modelled time horizon if more people discontinued treatment over time. The ERG's base-case assumption was that people stopping icosapent

ethyl would have the same clinical efficacy as the placebo group after 10 years. For people continuing treatment, the assumption was that the treatment effect would remain constant over the model time horizon. The committee considered that the clinical efficacy for people discontinuing could return to that of the placebo group at a timepoint earlier than 10 years. The committee acknowledged the limitations with the modelled scenarios but concluded it was reasonable to accept the ERGs assumptions that people stopping icosapent ethyl would lose treatment effect after 10 years and those continuing would maintain the treatment effect.

The treatment-independent non-cardiovascular-related death hazard ratios are acceptable

3.16 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 but people in the two prevention subgroups are not comparable. It added that diabetes and number of prior events were non-cardiovascular-related death modifiers. At its first meeting, the committee noted the non-cardiovascular-related death hazard ratios were uncertain and it would like to see evidence that diabetes and number of previous events are non-cardiovascular-related death modifiers. In response to consultation, the company updated its base case using treatment-independent non-cardiovascular-related death hazard ratios. It also provided evidence and clinical expert opinion to support its assessment that diabetes and number of previous events are non-cardiovascular-related death modifiers. The committee noted the

evidence and concluded the use of treatment-independent hazard ratios was consistent with its preference from the first meeting.

The company's model has uncertainties so the comparison with the validation model is also uncertain

3.17 Because of 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 after 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. At its first meeting, the committee concluded that there were unresolved uncertainties in the company's model that should be addressed before comparison with the validation model. In response to consultation, the company updated its time to event analysis (see section **Error! Reference source not found.**14) and used treatment-independent hazard ratios (see section **Error! Reference source not found.**) in its cost-effectiveness model. The committee noted there were still uncertainties about the company's model structure (see section 3.122) and how treatment effect after discontinuation was modelled (section **Error! Reference source not found.**5). The ERG also noted that it is unclear to what extent the validation model should be used to inform decisions in the company's model. The committee concluded that the

company's model remained uncertain and therefore the comparison with the validation model was uncertain.

Cost-effectiveness estimates

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

3.18 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 in terms of the population (see section 3.6)
- generalisability of the clinical trial results in terms of current management for cardiovascular disease and diabetes (see section **Error! Reference source not found.**)
- robustness of the treatment effect because of the mineral oil placebo (see section 3.9)
- differences in results from the REDUCE-IT and STRENGTH trials (see section 3.99)
- appropriateness of the company's model (see section 3.122)
- composite 5-point MACE outcome in the model (see section 3.133)
- most plausible time after which treatment effect may be lost after treatment is discontinued (see section 3.155).

Therefore, it agreed that an acceptable ICER would be below £20,000 per QALY gained.

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

3.19 The company's base case assumed no treatment waning for icosapent ethyl. After consultation, the company proposed a new list price which is considered confidential by the company. The company's new base-case ICER for icosapent ethyl compared with a stable dose of statins with or without ezetimibe was £19,848 per QALY gained for the secondary prevention group. The ERG's base case included a 10-year treatment reduction after discontinuation effect and its base-case ICER was £22,609 per QALY gained. The committee preferred the scenario with a 10-year treatment effect reduction after discontinuation and the treatment effect of icosapent ethyl was reduced by 7%. This resulted in a committee-preferred ICER of £34,067 per QALY gained. The committee recalled from its first meeting 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. The company did not submit any analyses for the primary prevention subgroup after consultation. The committee concluded that icosapent ethyl is not cost effective in the primary or secondary prevention populations.

Other factors

The committee considered potential equality issues in its decision making

3.20 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

3.21 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

3.22 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

3.23 The committee noted uncertainty in the clinical effectiveness evidence for icosapent ethyl because of the mineral oil placebo in the REDUCE-IT trial (see section 3.9). It also noted concerns about the generalisability of the trial results to the NHS in England (see sections 3.6 and 3.7). It was concerned about the company's modelling approach (see section 3.122), including how the treatment effect after discontinuation was modelled (section 3.155) and the composite outcome (see section 3.133). The

committee recalled its preferred ICER was higher than what NICE normally considers a cost-effective use of NHS resources. 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 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
March 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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