NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Icosapent ethyl is recommended as an option for reducing the risk of cardiovascular events in adults. It is recommended if they have a high risk of cardiovascular events and raised fasting triglycerides (1.7 mmol/litre or above) and are taking statins, but only if they have:

- established cardiovascular disease (secondary prevention), defined as a history of any of the following:
  - acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation)
  - coronary or other arterial revascularisation procedures
  - coronary heart disease
  - ischaemic stroke
  - peripheral arterial disease, and
- low-density lipoprotein cholesterol (LDL-C) levels above 1.04 mmol/litre and below or equal to 2.60 mmol/litre.

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 controlled levels of LDL-C but raised levels of triglycerides. Icosapent ethyl is licensed for people taking statins who have raised triglycerides and a high risk of cardiovascular events, and who have either:

- established cardiovascular disease (secondary prevention), or

- diabetes and at least one other cardiovascular risk factor (primary prevention).

Clinical trial evidence suggests that icosapent ethyl reduces the risk of cardiovascular events, compared with placebo, in people with raised fasting triglycerides (1.7 mmol/litre or above) who are taking statins. The trial only included people with LDL-C levels above 1.04 mmol/litre and below or equal to 2.60 mmol/litre.

The cost-effectiveness estimates for icosapent ethyl are uncertain. Icosapent ethyl is unlikely to be cost effective for primary prevention, so it is not recommended for this. But the most likely cost-effectiveness estimates for secondary prevention are within what NICE normally considers an acceptable use of NHS resources. So, icosapent ethyl is recommended for secondary prevention in people with LDL-C levels above 1.04 mmol/litre and below or equal to 2.60 mmol/litre.

People must be taking a statin to have icosapent ethyl. People who cannot have statins are not covered by icosapent ethyl's marketing authorisation, so NICE cannot make any recommendations in this area.

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 on other cardiovascular risk factor'.

Dosage in the marketing authorisation

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

Price

2.3 Icosapent ethyl costs £144.21 per pack of 120 capsules (excluding 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, 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 help to reduce the risk of cardiovascular events. The patient expert noted the importance of having 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 low-density lipoprotein cholesterol (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 below or equal to 2.60 mmol/litre. A clinical expert noted that there are people younger than 45 who have cardiovascular disease and elevated fasting 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 company highlighted that these analyses did not include adjusting for potential confounders or multiple comparisons. The committee was aware that restricting by age may

result in an equalities issue because age is a protected characteristic. The committee concluded that 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. This would ensure its recommendation was based on the available evidence.

It is appropriate to consider the effects of icosapent ethyl only 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. People in the secondary prevention group were aged 45 and older with established cardiovascular disease. The committee noted that NICE's technology appraisal guidance on alirocumab (TA393), evolocumab (TA394) and inclisiran (TA733) defined high risk of cardiovascular disease as a history of any of the following:

- a previous cardiovascular event, including acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation)
- previous coronary or other arterial revascularisation procedures
- coronary heart disease
- ischaemic stroke
- peripheral arterial disease.

In response to the first consultation, the company provided analyses that focused only on the secondary prevention subgroup. The committee noted that icosapent ethyl was unlikely to be cost effective in the primary prevention subgroup, because the cost-effectiveness estimates presented at the first committee meeting were substantially higher than the range normally considered an acceptable use of NHS resources. It concluded that it was appropriate to focus on the effects of icosapent ethyl for the secondary prevention subgroup. This includes people with diabetes who have established cardiovascular disease.

Clinical evidence

The REDUCE-IT trial 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 who had statins with or without ezetimibe, fasting triglyceride levels of 1.53 mmol/litre or more and below 5.64 mmol/litre, and LDL-C levels of more than 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 (see section 3.5). The primary endpoint was time from randomisation to the first occurrence of any component of the major adverse cardiovascular event (MACE) composite outcome. This comprised 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, because some family backgrounds were underrepresented. They noted that people with South Asian family backgrounds may benefit more from icosapent ethyl. The company compared the baseline characteristics of the secondary prevention subgroup with a similar population 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 BMI and systolic blood pressure were similar between REDUCE-IT and Steen et al. However, the ERG noted that there were substantial differences between REDUCE-IT and Steen et al. that might modify the treatment effect. The mean age was higher in Steen et al. and the percentage of male patients was lower. There were also differences in comorbidities. In response to consultation, the company highlighted that the populations in England and REDUCE-IT had similar distributions by ethnic group. The company also stated that in REDUCE-IT, there was no interaction between the efficacy of icosapent ethyl in reducing the risk of cardiovascular events according to ethnicity ('white' HR 0.77, 95%

CI 0.69 to 0.85, 'non-white' HR 0.60, 95% CI 0.43 to 0.83). It stated that an advisory board of 9 UK clinical experts considered the trial data would be generalisable to the UK population. The clinical adviser to NHS England noted that several treatments available in the NHS, such as SGLT2 inhibitors and GLP-1 agonists, were used by only a small proportion of people in REDUCE-IT. The clinical adviser explained that the change in treatment landscape in the NHS in England since the trial began makes the generalisability of REDUCE-IT to current practice uncertain. The company stated that the use of SGLT2 inhibitors and GLP-1 agonists in the trial was consistent with clinical practice at the time of the trial. It also noted that people who do not have diabetes would not necessarily be able to have these treatments. The committee concluded that REDUCE-IT may not fully represent NHS clinical practice, which increases uncertainty around the generalisability of the results.

There is uncertainty in the trial results because icosapent ethyl's mechanism of action is not fully understood

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 to reduce 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. It was also larger than that reported by an earlier trial (STRENGTH) of a drug with a similar mechanism of action to icosapent ethyl (see section 3.8). In response to consultation, the company stated that the mechanism of action is likely multifactorial and that icosapent ethyl can positively alter the development, progression and stabilisation of atherosclerotic plaque. It stated that triglyceride reduction only played a minor role in the reduction in the risk of cardiovascular events associated with icosapent ethyl. 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. This added uncertainty to the trial's results because the difference in benefit compared with STRENGTH had not been fully explained.

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

3.8 The placebo group in REDUCE-IT had 4 g of light mineral oil per day. 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 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, but not the same as, icosapent ethyl) with a corn oil placebo. The ERG explained that a 2021 paper by Doi et al. comparing REDUCE-IT with STRENGTH suggested the differences in results might be partially explained by differences in placebo comparators. But the ERG 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 that it is likely that mineral oil at the quantities used as placebos does not significantly affect the conclusion of REDUCE-IT. However, the ERG noted that this systematic review had some limitations and one of the co-authors was employed by the company. In response to consultation, the company acknowledged 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, 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. In response to consultation the company also highlighted that the drug in STRENGTH was different to icosapent ethyl because of different proportions of docosahexaenoic acid and eicosapentaenoic acid. So, comparing the results from the 2 trials was not appropriate. 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 potential negative effect of the mineral oil placebo.

It is appropriate to consider scenarios for an estimated possible reduction in treatment effect from 1.5% to 3%

3.9 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. This estimate was based on the 2021 paper by Doi et al. comparing the results of REDUCE-IT and STRENGTH. The committee was aware that the company provided the analyses done by the Food and Drug Administration (FDA) in the US to the European Medicines Agency based on the 3-point MACE outcome assuming that the potential negative effect of mineral oil on MACE events was between 0.3% and 3%. The committee also noted that the Doi et al. 2021 paper commented that there was an unexplained additional 13% benefit in REDUCE-IT. In response to the first 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 considered that the range of 7% to 13% was not plausible because it was based on a single simulated Danish observational study. 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 which percentage reduction in treatment effect was more plausible. The committee was aware that the European public assessment report on icosapent ethyl notes that a 10% putative negative effect of mineral oil would be a worst-case scenario but likely an overestimation. In response to the second consultation, the company

presented an analysis replicating a Cox regression model made by the FDA to examine the effects of high-sensitivity C-reactive protein and LDL-C on the relative benefit of icosapent ethyl. It presented a propensity score matched approach to the Cox regression analysis to account for overlapping effects of the biomarkers. It also presented an analysis exploring the relationship between on-treatment serum active drug concentration and cardiovascular outcomes to explore the effects on cardiovascular risk that are independent of serum eicosapentaenoic acid levels. The company considers the results of these analyses to be confidential so they cannot be reported here. On the basis of these analyses, the company updated its base-case model to include a 1.5% reduced treatment effect for icosapent ethyl. Considering the company's analyses and the conclusion of the European Medicines Agency, the committee concluded that it would be appropriate to consider scenarios estimating a possible reduction in treatment effect from 1.5% to 3%.

Icosapent ethyl has manageable adverse events

3.10 In REDUCE-IT, similar proportions of people having icosapent ethyl (81.8%) and placebo (81.3%) reported adverse events. The clinical experts noted that 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). The company stated 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

3.11 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 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. 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 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 that the company's model did not explicitly model nonfatal cardiovascular events and used a 1-day cycle length. 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 considered that these comments were insufficient

justification for the model structure and uncertainty remains. The company provided a comparison of the model-estimated survival and mortality from REDUCE-IT. The committee noted that the model appeared to overestimate mortality in both the placebo and icosapent ethyl groups at 5 years. 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

3.12 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 in the intention to treat population, the hazard ratios for cardiovascular death (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 combining time to composite event with the proportion of each event in the composite outcome. The clinical experts commented that using a composite MACE outcome is common for large clinical trials but one expert said that there was some debate about whether 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 also 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 separation of icosapent ethyl and placebo curves at around 1 to 2 years. This 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 between the individual events and the composite. The committee welcomed the additional information from the company but concluded that using the composite outcome in the model increased uncertainty.

It is implausible that there is no loss of treatment effect at treatment discontinuation

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 loss of treatment effect at discontinuation. The company commented that similar technology appraisals did not include loss of treatment effect, including TA393, TA394 and TA733. The company provided an analysis of the treatment effect over time, which showed that it did not decrease during the follow-up period of REDUCE-IT. The clinical expert commented that given the absence of longer-term data it is difficult to determine the appropriateness of an assumption of treatment effect loss. 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 loss of treatment effect 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 that 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 committee noted that in the recent related appraisal of bempedoic acid with 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 TA393, 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 many people had 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 company highlighted that follow-up was longer in REDUCE-IT and so it would be expected that more people would discontinue treatment. The committee noted that assumptions of complete continuation and no loss of treatment effect were also used in TA733. The committee commented that the icosapent ethyl appraisal had different considerations to those previous appraisals. It considered that there was large 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 committee concluded that it was implausible that the treatment effect would not reduce at any point after discontinuation.

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

3.14 The company's base case did not apply a loss of treatment effect. However, the company 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 at discontinuation, which was not clinically plausible. The committee agreed that the way in which the loss of treatment effect had been modelled was potentially biased against icosapent ethyl. This was mainly because it was implausible that all avoided events would occur at

treatment discontinuation, but also because the efficacy curves for people staying on treatment included some people who had stopped treatment in the trial. The ERG's base-case included the company's scenario where 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 acknowledged the limitations with the modelled scenarios but considered it reasonable to accept the scenario in which people stopping icosapent ethyl would lose treatment effect after 10 years and those continuing would maintain the treatment effect. However, it acknowledged that the true cost-effectiveness results would likely be lower than in the scenarios presented, had the loss of treatment effect been modelled more appropriately.

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

3.15 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 the 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 a disutility associated with an acute event 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 had different structures but produced similar clinical estimates. The committee noted there were still uncertainties about the company's model structure (see section 3.11) and how treatment effect after discontinuation was modelled (see section 3.13). The ERG also noted that it was 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 towards the lower end of the range normally considered a cost-effective use of NHS resources

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. Because of the high level of uncertainty in the clinical and economic evidence, the committee agreed that an acceptable ICER would be towards the lower end of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

The most plausible ICER is between £21,750 and £24,821 per QALY gained

3.17 After the second consultation, the company's base-case ICER for icosapent ethyl compared with a stable dose of statins with or without ezetimibe was £20,000 per QALY gained for the secondary prevention group. The company's base case assumed no loss of treatment effect for icosapent ethyl but did include a 1.5% treatment effect reduction to account for the possible effects of the mineral oil placebo. The ERG's base case included a loss of treatment effect for those discontinuing after 10 years but did not include a reduction in treatment effect for the mineral oil placebo. The ERG's base-case ICER was £21,062 per QALY gained. The ERG presented scenario analyses including a 0%, 1.5%, 3% or 7% treatment effect reduction to adjust for the possible effect of mineral oil. It also presented scenario analyses including a loss of treatment effect on discontinuation after 5 or 10 years, or not at all. The committee considered that the scenarios including a reduction of treatment effect of

1.5% and 3% (see section 3.9) and a loss of treatment effect on discontinuation at 10 years (see section 3.14) were the most plausible scenarios. However, it considered that the ICERs that included a loss of treatment effect on discontinuation were likely too high, because of the way this had been modelled. So, the committee also considered a scenario with a 3% reduction in treatment effect and no loss of treatment effect on discontinuation. Therefore, the committee considered that the most plausible ICER was between £21,750 and £24,821 per QALY gained.

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 benefits associated with icosapent ethyl over those already included in the QALY calculations.

Conclusion

Icosapent ethyl is 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 in the REDUCE-IT trial (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 3.11), including how the treatment effect after discontinuation was modelled (see section 3.13) and the composite outcome (see section 3.12). Nevertheless, the most plausible ICER was towards the lower end of the range of what NICE normally considers a cost-effective use of NHS resources. Therefore, the committee recommended icosapent ethyl for reducing the risk of cardiovascular events in people with raised fasting triglycerides (1.7 mmol/litre or more) who are having statins and have established cardiovascular disease. Established cardiovascular disease is defined in line with the definition of high-risk cardiovascular disease in NICE's technology appraisal guidance on alirocumab, evolocumab and inclisiran (see section 3.5). Icosapent ethyl is recommended for people with LDL-C levels above 1.04 mmol/litre and below or equal to 2.60 mmol/litre, in line with the clinical evidence from REDUCE-IT (see section 3.4).

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has raised triglycerides and the doctor responsible for their care thinks that icosapent ethyl is the right treatment to reduce the risk of cardiovascular events, it should be available for use, in line with NICE's recommendations.

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.

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