5.07 ICOSAPENT ETHYL, Capsule 1 g, Vazkepa®, SEQIRUS (AUSTRALIA) PTY LTD.

1 Purpose of submission

1.1 The Category 1 submission requested a General Schedule Authority Required (STREAMLINED) listing of icosapent ethyl for the treatment of patients with atherosclerotic cardiovascular disease (ASCVD) and elevated triglycerides.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus standard of care.

Table 1: Key components of the clinical issue addressed in the submission

Component	Description
Population	Adult patients with atherosclerotic cardiovascular disease (ASCVD), a triglyceride level ≥1.7 mmol/L and <5.6 mmol/L, and an LDL cholesterol level >1.0 mmol/L and ≤2.6 mmol/L, who are receiving the maximum tolerated dose of a statin.
Intervention	Icosapent ethyl 2 g twice daily
Comparator	Standard of care
Outcomes	Nonfatal MI, nonfatal stroke, hospitalisation for unstable angina, coronary revascularisation, cardiovascular death, all-cause mortality, lipid levels, adverse events.
Clinical claim	Icosapent ethyl is superior to standard of care in reducing the risk of major adverse cardiovascular events with an inferior but manageable safety profile.

Source: Table 1.1.1, p25 of the submission.
Abbreviations: LDL, low-density lipoprotein cholesterol; MI, myocardial infarction.

2 Background

Registration status

2.1 Icosapent ethyl was registered on the ARTG on 8 November 2022 and is indicated to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥1.7 mmol/L) and

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

Previous PBAC consideration

2.2 The PBAC has not previously considered icosapent ethyl (an ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA)) for any indication. A submission for an omega-3 fatty acid formulation of EPA and docosahexaenoic acid (DHA) ethyl esters for use in secondary prevention after myocardial infarction was considered by the PBAC at the November 2010 PBAC meeting.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat and PBAC are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№. of Rpts	Available brands
ICOSAPENT ETHYL					
Icosapent ethyl ~~1 g~~ *998 mg* capsule, 120	$[redacted]	1	120	5	Vazkepa

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (STREAMLINED)
Administrative Advice: *No increase in the maximum quantity or number of units may be authorised.*
Administrative Advice: *No increase in the maximum number of repeats may be authorised.*
~~**Condition**~~ ***Indication:*** Established atherosclerotic cardiovascular disease with hypertriglyceridaemia
Treatment Phase: ~~Initiation~~ *Initial treatment*
Clinical criteria:
The treatment must be in combination with dietary therapy and exercise
AND
Clinical criteria:
Patient must have *at least one of (i)* coronary heart disease, ~~AND/OR~~ *(ii)* cerebrovascular disease, ~~AND/OR~~ *(iii)* peripheral vascular disease
AND
Clinical criteria
~~Treatment must be co-administered~~ *Patient must be treated* with ~~the maximum tolerated~~ *a stable* dose of a HMG CoA reductase inhibitor (statin) *to achieve target secondary prevention LDL-c levels for at least 12 consecutive weeks, OR*
Patient must have developed clinically important product-related adverse events necessitating withdrawal of statin treatment; OR
Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information
AND
Clinical criteria:
Patient must have LDL cholesterol level~~s~~ between 1.0 mmol/L and 2.6 mmol/L
AND
Clinical criteria
Patient must have *fasting* triglyceride levels between ~~of~~ 1.7 mmol/L and 5.6 mmol/L
Prescribing instructions: *The qualifying* fasting triglyceride level and *LDL cholesterol level following at least 12 consecutive weeks of combined treatment with a statin, dietary therapy and exercise should be documented in the patient's medical records and must be no more than 8 weeks old.*
Prescribing instructions: *A clinically important product-related adverse event is defined as follows:* *(i) Severe myalgia (muscle symptoms without creatine kinase elevation) which is proven to be temporally associated with statin treatment; or*

(ii) Myositis (clinically important creatine kinase elevation, with or without muscle symptoms) demonstrated by results twice the upper limit of normal on a single reading or a rising pattern on consecutive measurements and which is unexplained by other causes; or *(iii) Unexplained, persistent elevations of serum transaminases (greater than 3 times the upper limit of normal) during treatment with a statin.*

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners ☐Nurse practitioners
Restriction type: ☒Authority Required (STREAMLINED
~~**Condition**~~ ***Indication:*** Established atherosclerotic cardiovascular disease with hypertriglyceridaemia
Treatment Phase: ~~Continuation~~ *Continuing treatment*
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
The treatment must be in combination with dietary therapy and exercise
~~**AND**~~
~~**Clinical criteria:**~~
~~Treatment must be co-administered with the maximum tolerated dose of an HMG CoA reductase inhibitor (statin)~~

Note: The dispensed price for maximum quantity was updated during the evaluation to incorporate July 2023 fees and mark-ups (a DPMQ of $[redacted] was used in the submission)

3.2 The proposed initial treatment restriction is narrower than the TGA indication, as it does not include primary prevention (i.e., treatment of patients with diabetes and at least one other cardiovascular risk factor); limits treatment to patients with a maximum triglyceride level of 5.6 mmol/L; limits treatment to patients with specified low density lipoprotein (LDL) cholesterol levels (1.0-2.6 mmol/L); requires patients to be receiving the maximum dose of a statin (versus 'statin-treated'); and requires treatment to be in conjunction with dietary therapy and exercise. The rationale for selecting the secondary prevention population was that this population has the highest baseline risk of experiencing cardiovascular events and therefore has the greatest clinical need for therapeutic options.

3.3 The proposed restriction does not preclude use in combination with LDL cholesterol-lowering treatments such as ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. This appears to be appropriate given the proposed place in therapy of icosapent ethyl. However, the comparative clinical benefit and cost-effectiveness of coadministration of icosapent ethyl and either ezetimibe or PCSK9 inhibitors was not considered in this submission. The ESC also noted that the proposed restriction does not preclude use in combination with other agents that lower triglycerides such as fibrates and niacin. The ESC considered that, although there was no specific clinical data regarding combination therapy, these agents should not be co-administered. The DUSC further noted that evidence presented by Graverson et al. (2016) suggests that supplementation with n-3 polyunsaturated fatty acids reduced plasma PCSK9 inhibitor levels indicating that coadministration of a PCSK9 inhibitor with icosapent ethyl may reduce the efficacy of the PCSK9 inhibitor.

3.4 The proposed restriction requires patients to have one of coronary heart disease, cerebrovascular disease or peripheral vascular disease. The ESC considered that it may be appropriate to include specific diagnostic criteria for these conditions in the restriction.

3.5 The proposed restriction requires patients to be on the maximum tolerated dose of a statin. The ESC noted that this was narrower than the clinical trial criteria, which specified that patients were receiving a stable dose of statin therapy and had an LDL cholesterol of > 1.04 mmol/L and ≤ 2.60 mmol/L. The ESC also noted that 96% of trial patients were receiving medium to high intensity statins. The ESC considered that specifying that patients were receiving the maximum tolerated dose of statin may not be necessary and instead that it might be more appropriate to specify that patients were receiving a medium to high intensity statin therapy and achieving guideline directed secondary prevention LDL cholesterol targets. The ESC felt it was appropriate to remain silent on other hypolipidemic therapies.

3.6 The proposed restriction does not explicitly include treatment of patients with statin intolerance, or patients who are contraindicated to statins. Given the different postulated mechanism of action of icosapent ethyl, the ESC considered that it was not reasonable to exclude patients who have developed an adverse event necessitating withdrawal of statin treatment, or patients who are contraindicated to treatment with a statin.

3.7 Based on the proposed LDL cholesterol criteria, patients with LDL cholesterol < 1.0 mmol/L would not be eligible for treatment with icosapent ethyl. While an LDL cholesterol level of 1.04 to 2.6 mmol/L is consistent with the inclusion criteria for the REDUCE-IT trial, it may not be reasonable to exclude patients with an LDL cholesterol of < 1.0 mmol/L from access to PBS treatment with icosapent ethyl. The Pre-Sub-Committee Response (PSCR) noted that icosapent ethyl resulted in a consistent benefit across the range of baseline LDL cholesterol levels.

3.8 Based on the proposed triglyceride criteria, patients with a triglyceride level > 5.6 mmol/L would not be eligible for treatment with icosapent ethyl. While this is consistent with the eligibility criteria for the REDUCE-IT trial, it may not be reasonable to exclude this group of patients from access to PBS treatment with icosapent ethyl. The ESC considered that, given the uncertain mechanism of action of icosapent ethyl and the evidence that actual triglyceride level lowering was unlikely to be an important component, it would be preferable to maintain the clinical trial inclusion criteria in the restriction.

3.9 The proposed restriction allows for prescribing by general practitioners. While this is consistent with the PBS restrictions for statins and ezetimibe, it differs from the restrictions for the PCSK9 inhibitors, which specify that treatment must be prescribed by a specialist physician or by a physician who has consulted a specialist physician.

3.10 There is potential for use outside of the proposed restriction among patients who are not using the maximum tolerated dose of a statin (or receiving medium to high

intensity statin therapy as per paragraph 3.5), and patients who do not meet the LDL and triglyceride requirements. The DUSC further noted that there are clinical trials underway exploring the use of icosapent ethyl or similar fatty acids for other indications such as major depression, bipolar disease, prodromal symptoms of schizophrenia, prevention of coronavirus disease (COVID-19) infection and other upper respiratory tract infections, metastatic triple negative breast cancer, colon cancers, and neurodegenerative disorders such Huntington and Alzheimer disease. The DUSC considered that there may be a high risk of leakage into these indications due to these ongoing trials or result in higher initial uptake rates.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 ASCVD includes coronary artery disease, cerebrovascular disease, aortic disease, and other vascular diseases such as peripheral artery disease and renovascular disease. Patients with established ASCVD are at high risk of future cardiovascular events, including myocardial infarction and stroke.

4.2 Hypertriglyceridaemia, defined as a triglyceride level ≥ 1.7 mmol/L, is associated with an increase in remnant cholesterol, a decrease in high-density lipoprotein cholesterol (HDL-C), and an increase in LDL particles with a change in morphology to small, dense particles. Epidemiological and Mendelian randomisation studies suggest that triglyceride elevation is independently associated with increased ASCVD risk (Virani et al., 2021). Triglyceride levels ≥5.6 mmol/L are associated with an increased risk of acute pancreatitis.

4.3 The population targeted in the submission are patients with established ASCVD and adequately controlled (at the time the study was conducted) LDL cholesterol levels (1.0-2.6 mmol/L), who have mild to moderately elevated triglycerides (1.7-5.6 mmol/L) despite treatment with a statin. Patients with mild to moderate triglyceride levels and LDL cholesterol levels between 1.8 and 2.6 mmol/L may also be candidates for additional LDL cholesterol-lowering therapies, such as ezetimibe and PCSK9 inhibitors, for the reduction of cardiovascular risk. These treatments are also associated with modest triglyceride lowering effects.

4.4 Icosapent ethyl is an ethyl ester of eicosapentaenoic acid (EPA), an omega-3 fatty acid. The mechanisms of action contributing to the reduction in cardiovascular events with icosapent ethyl are not completely understood, but may include improvement in the lipoprotein profile with a reduction of triglyceride-rich lipoproteins, anti-inflammatory and antioxidant effects, changes in plaque structure and vulnerability (e.g. reduction of macrophage accumulation, improved endothelial function, increased fibrous cap thickness/stability) and antiplatelet effects. A 2020 consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology suggested that the improvement in cardiovascular outcomes

associated with icosapent ethyl may be largely, if not entirely, independent of the triglyceride lowering effects.

4.5 The recommended daily dose of icosapent ethyl is 4 g daily (i.e., two x 1 g capsules twice daily). Treatment with icosapent ethyl is ongoing. The submission stated that treatment with icosapent ethyl would be in conjunction with diet and lifestyle interventions, and optimisation of LDL cholesterol-lowering using the maximum tolerated dose of a statin, plus other LDL cholesterol-lowering therapies as required. The submission argued that icosapent ethyl would be used in parallel with LDL cholesterol-lowering treatments and as such, the addition of icosapent ethyl to the PBS would not result in substitution for any other therapies. The ESC advised that there may be substitution of fibrates (fenofibrate or gemfibrozil) and potentially also of nicotinic acid.

4.6 The ESC noted that there was a long history of trials studying the mechanism of action and effects of fish oils (e.g. JELIS, STRENGTH, MARINE, ANCHOR) and fibrates (e.g. BIP, LEADER, FIELD, ACCORD-Lipid, ACCORDION, Three City Study Cohort Elderly without CVD, ECLIPSE-REAL) in ASCVD which have provided variable results. The ESC noted that although fish oil trials have demonstrated that both EPA and DHA lower triglyceride levels, the benefits in terms of ASCVD were not conclusive. In terms of the fibrate trials, the ESC noted that the majority failed to reach their primary ASCVD endpoints.

4.7 The ESC noted there was only modest support for icosapent ethyl in treatment guidelines. The European Society of Cardiology Guidelines 2021[1] classed icosapent ethyl as a IIb treatment (IIb: usefulness/efficacy is less well established by evidence/opinion). The Guidelines recommended that in high risk or very high risk patients with triglycerides > 1.5 mmol/L (135 mg/dL) despite statin treatment and lifestyle measures, icosapent ethyl (2 x 2 g/day) may be considered in combination with a statin. Further, the American Heart Association (AHA)/American College of Cardiology (ACC) Multisociety Guideline for the Management of Patients with Chronic Coronary Disease 2023[2] stated that in patients with chronic coronary disease receiving statin therapy, the addition of dietary supplements containing omega-3 fatty acids, are not beneficial in reducing cardiovascular risk.

For more detail on PBAC's view, see section 7 PBAC outcome.

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[1] *European Heart Journal*, Volume 42, Issue 34, 7 September 2021, Pages 3227–3337, https://doi.org/10.1093/eurheartj/ehab484

[2] Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation. 2023;148:e9–e119. doi: 10.1161/CIR.0000000000001168

5 Comparator

5.1 The submission nominated standard of care (consisting of dietary modification, lifestyle interventions, and concomitant optimisation of LDL cholesterol lowering using a statin-based therapeutic regimen), as the main comparator. The main arguments provided in support of this nomination were that, for patients receiving treatment with statins, there are no other therapeutic options available to reduce cardiovascular risk in patients with elevated triglycerides. The ESC considered that standard of care is an appropriate comparator. However, the claim that there are no other therapeutic options available to reduce cardiovascular risk in patients with elevated triglycerides was not reasonable, given that available LDL cholesterol-lowering treatments such as ezetimibe and PCSK9 inhibitors may also cause a modest reduction in triglyceride levels.

5.2 The submission argued that other LDL cholesterol-lowering therapies such as ezetimibe and PCSK9 inhibitors are not relevant comparators on the basis that they would be used in parallel with icosapent ethyl (if required) to manage LDL levels. The ESC considered this assumption was reasonable, given that treatment with icosapent ethyl in the REDUCE-IT trial was not associated with reductions in LDL cholesterol levels, and patients at high cardiovascular risk with LDL cholesterol levels above treatment targets would still be eligible for LDL cholesterol-lowering therapies.

5.3 The submission argued that prescription omega-3 fatty acids are not a relevant comparator on the basis that there are no products currently listed on the PBS. The submission also noted that a November 2010 submission to PBAC for an EPA/DHA omega-3 fatty acid ester preparation for use in secondary prevention after myocardial infarction was rejected on the basis of inadequate clinical data to establish efficacy in the proposed Australian population and the associated highly uncertain cost-effectiveness ratio (Omega-3-acid ethyl esters, Public Summary Document (PSD), November 2010 PBAC meeting).

5.4 The submission argued that over-the-counter omega-3 fatty acid formulations were not relevant comparators for the following reasons:

- The 2021 American College of Cardiology guideline (Virani et al., 2021) states that non-prescription fish oil products have not been shown to improve cardiovascular outcomes and are not recommended for ASCVD risk reduction.
- Unlike prescription omega-3 fatty acid products, supplements are not approved by the TGA, and their manufacturing processes are not regulated to the same degree as the manufacturing process for prescription medications. There may be variability in the content and quality of these omega-3 fatty acid products.
- While a meta-analysis of 38 randomised controlled trials assessing the effects of omega-3 fatty acid products on cardiovascular outcomes (Khan et al., 2021) suggested a statistically significant reduction in cardiovascular mortality and major adverse cardiovascular events, much of the benefit was driven by the

results of the icosapent ethyl arm of the REDUCE-IT trial. Additionally, the authors concluded that EPA was more effective than EPA + DHA, and only at higher doses.

- The European Medicines Agency (EMA) previously stated that omega-3 fatty acid medicines containing a combination of DHA and EPA at a dose of 1 g per day are not effective in preventing further problems with the heart and blood vessels in patients who have had a heart attack (EMA public health communication 186168, March 2019).

5.5 In the November 2010 consideration of the EPA/DHA omega-3 fatty acid ester preparation for use in secondary prevention after myocardial infarction, the PBAC considered that over-the-counter fish oil preparations or a diet high in oily fish may be potential comparators (Omega-3-acid ethyl esters, PSD, November 2010 PBAC meeting). The PSCR stated that several international guidelines, multiple large-scale studies (ASCEND, VITAL and OMEMI) and a recent meta-analysis (Khan et al, 2021) concluded that non-prescription fish oils do not demonstrate significant reductions in cardiovascular events. The ESC agreed with the submission that over-the-counter fish oil preparations or a diet high in oily fish are not relevant comparators in the context of the current submission for icosapent ethyl.

5.6 The submission did not consider fibrates to be a relevant comparator on the basis that the effectiveness of fibrates in combination with statins in preventing cardiovascular events has not been convincingly demonstrated and use in combination with statins increases the risk of adverse events, particularly myalgias, myositis and rhabdomyolysis. The submission argued that clinical practice guidelines predominantly recommend fibrates in patients with severe hypertriglyceridaemia for the prevention of pancreatitis. This argument appeared to be reasonable. However, given the evidence of a lack of effect for fibrates when used in combination with a statin, there may be potential for icosapent ethyl to substitute for fibrates which are sometimes prescribed for the reduction of cardiovascular events in patients with hypertriglyceridaemia.

5.7 The submission argued that nicotinic acid is not a relevant comparator on the basis that combination treatment with nicotinic acid and a statin was not associated with an improvement in cardiovascular outcomes compared to a statin alone in the AIM-HIGH trial, and treatment with nicotinic acid is associated with a high incidence of adverse events. The exclusion of nicotinic acid as a comparator appeared to be reasonable given the lack of clinical evidence to support its use in combination with a statin, and the limited use of nicotinic acid in Australian clinical practice (Brett et al., 2021).

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician described that there was evolving knowledge of the pleiotropic mechanism of action of icosapent ethyl and how this leads to potential beneficial effects on cardiovascular endpoints, as seen in the REDUCE-IT trial. The mechanism of action was speculated to be due to icosapent ethyl mediating the eicosapentaenoic acid/arachidonic acid ratio and triglyceride levels which reduces atherosclerosis and plaque volume and improves plaque stability, impacting coronary artery plaque development, progression and rupture. The clinician also discussed how the drug would be used in practice, stating that there was robust evidence of the benefits of treatment across a broad population, that icosapent ethyl had a good safety profile, noting that there was some peripheral oedema, constipation and atrial fibrillation associated with icosapent ethyl, and that it would provide an additional clinical option for patients with secondary cardiovascular disease. Noting the high pill burden of treatment with icosapent ethyl, the clinician stated that the affected population was well motivated to adhere to medication. The PBAC considered that the hearing was informative.

6.2 The consultant for the sponsor clarified the rationale for the differential censoring in the economic model between the icosapent and the placebo arms. The model included censoring in the icosapent ethyl treatment arm when patients discontinued treatment, which meant the treatment effect reverted to placebo rates. This differed to the trial data. The placebo arm was uncensored in the model. The different approaches in each arm were argued to be appropriate as the net effect was then balanced.

Consumer comments

6.3 The PBAC noted and welcomed the input from health care professionals (4) via the Consumer Comments facility on the PBS website. The comments described the benefits of treatment with icosapent ethyl, including the lowering of triglyceride levels and the risk of cardiovascular events in those with ASCVD, as well as reducing overall mortality rates. The comments also noted the minimal side effects associated with the drug and the quality of life benefits. The PBAC considered there was a common misunderstanding from some health professionals that icosapent ethyl is a triglyceride lowering therapy; the mechanism of action was noted by others to involve multiple pathways, as was described in the hearing.

Clinical trials

6.4 The submission was based on one head-to-head randomised trial (REDUCE-IT) comparing icosapent ethyl to placebo. The literature search excluded studies that assessed treatment with mixed EPA and DHA omega-3 fatty acid preparations, studies assessing EPA at lower doses, and studies that did not report cardiovascular outcomes.

The narrow search strategy likely resulted in exclusion of potentially informative studies.

6.5 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
REDUCE-IT	Multi-Center, Prospective, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effect of AMR101 on Cardiovascular Health and Mortality in Hypertriglyceridemic Patients with Cardiovascular Disease or at High Risk for Cardiovascular Disease. REDUCE-ITTM (Reduction of Cardiovascular Events with EPA – Intervention Trial).	Clinical study report, 27 February 2019.
	Bhatt DL, Steg PG, Miller M, Brinton EA et. al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia.	*N Engl J Med.* 2019; 380(1): 11-22.
	Bhatt DL, Steg PG, Miller M, Brinton EA *et al*. Effects of Icosapent Ethyl on Total Ischemic Events: from REDUCE-IT.	*J Am Coll Cardiol.* 2019; 73(22): 2791-2802.
	Gaba P, Bhatt DL, Steg PG, Miller, M *et al*. Prevention of Cardiovascular Events and Mortality With Icosapent Ethyl in Patients With Prior Myocardial Infarction.	*J Am Coll Cardiol.* 2022; 79(17): 1660-1671.
	Gaba P, Bhatt DL, Giugliano RP, Steg PG *et al*. Comparative Reductions in Investigator-Reported and Adjudicated Ischemic Events in REDUCE-IT.	*J Am Coll Cardiol.* 2021; 78(15): 1525-1537.
	Majithia A, Bhatt DL, Friedman AN, Miller M *et al*. Benefits of Icosapent Ethyl Across the Range of Kidney Function in Patients With Established Cardiovascular Disease or Diabetes: REDUCE-IT RENAL.	*Circulation 2021;* 144(22),:1750-1759.
	Miller M, Bhatt DL, Steg PG, Brinton EA *et al*. Potential Effects of Icosapent Ethyl on Cardiovascular Outcomes in Cigarette Smokers: REDUCE-IT Smoking.	*Eur Heart J Cardiovasc Pharmacother* 2023; 9(2): 129-137.
	Olshansky B, Bhatt DL, Miller M, Steg PG *et al*. Cardiovascular Benefits of Icosapent Ethyl in Patients With and Without Atrial Fibrillation in REDUCE-IT.	*J Am Heart Assoc.* 2023; 12(5): e026756.
	Peterson BE, Bhatt DL, Steg PG, Miller M *et al*. Treatment With Icosapent Ethyl to Reduce Ischemic Events in Patients With Prior Percutaneous Coronary Intervention: insights From REDUCE-IT PCI.	*J Am Heart Assoc.* 2022; 11(6): e022937.
	Peterson BE, Bhatt DL, Steg PG, Miller M *et al*. Reduction in Revascularization With Icosapent Ethyl Insights From REDUCE-IT Revascularization Analyses.	*Circulation* 2021; 143(1): 33-44.
	Ridker PM, Rifai N, MacFadyen J, Glynn RJ *et al*. Effects of Randomized Treatment With Icosapent Ethyl and a Mineral Oil Comparator on Interleukin-1β, Interleukin-6, C-Reactive Protein, Oxidized Low-Density Lipoprotein Cholesterol, Homocysteine, Lipoprotein(a), and Lipoprotein-Associated Phospholipase A2: a REDUCE-IT Biomarker Substudy.	*Circulation* 2022; 146(5): 372-379.
	Selvaraj S, Bhatt DL, Steg PG, Miller M *et al*. Impact of Icosapent Ethyl on Cardiovascular Risk Reduction in Patients With Heart Failure in REDUCE-IT.	*J Am Heart Assoc.* 2022; 11(7): e024999.
	Verma S, Bhatt DL, Steg PG, Miller M *et al*. Icosapent Ethyl Reduces Ischemic Events in Patients With a History of Previous Coronary Artery Bypass Grafting: REDUCE-IT CABG.	*Circulation* 2021; 144(23): 1845-1855.

Source: Table 2.2.2, pp46-47 of the submission.
Selected conference abstract citations omitted.

6.6 The key features of the included trial (REDUCE-IT) are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Icosapent ethyl versus placebo						
REDUCE-IT	8,179	Randomised, placebo-controlled trial; median follow-up 4.9 years	Low	- Secondary prevention cohort: age ≥45 years with documented coronary artery disease, cerebrovascular or carotid disease, or peripheral arterial disease - Primary prevention cohort: age ≥50 years with type 1 or 2 diabetes mellitus (requiring medication) and one additional risk factor for cardiovascular disease. - Fasting triglyceride levels ≥1.53 mmol/L and <5.64 mmol/L[a] - LDL cholesterol >1.04 mmol/L and ≤2.60 mmol/L - On stable therapy with a statin (with or without ezetimibe).	- 5-point MACE composite (primary) - 3-point MACE composite (key secondary) - Composite of CV death or nonfatal MI - Fatal or nonfatal MI - Non-elective coronary revascularisation - CV death - Unstable angina requiring hospitalisation - Fatal or nonfatal stroke - Composite of total mortality, nonfatal MI or nonfatal stroke - Total mortality - Change in lipid levels - Adverse events	- Nonfatal stroke - Nonfatal MI - CV death - Non-CV death - Coronary revascularisation - Hospitalisation for unstable angina - Time to treatment discontinuation

Source: Section 3, pp100-149 of the submission.

Abbreviations: CV, cardiovascular; LDL, low-density lipoprotein; MACE, major adverse cardiac event; MI, myocardial infarction.

[a] A protocol amendment increased the lower end of the fasting triglyceride level from ≥135 mg/dL (1.53 mmol/L) to ≥200 mg/dL (2.26 mmol/L).

6.7 The REDUCE-IT trial had a low risk of bias. The REDUCE-IT trial included two groups of patients: patients aged ≥45 years with documented coronary artery disease, cerebrovascular or carotid disease, or peripheral arterial disease (secondary prevention population); and patients aged ≥ 50 years with type 1 or 2 diabetes mellitus (requiring medication) and one additional risk factor for cardiovascular disease (primary prevention population). To align with the proposed PBS population with established ASCVD, the submission was based on the results of secondary prevention population. Analyses based on the secondary prevention population were conducted post hoc and were at a higher risk of bias.

6.8 The ESC noted that since the trial was published, concerns have been raised regarding the use of mineral oil as the placebo. In particular, it has been questioned whether increases in biomarker levels (LDL cholesterol, apolipoprotein B, high sensitive C-reactive protein) in the placebo arm of the trial may be related to the use of mineral oil, likely through partial interference with statin absorption. It has been noted that these considerations impact the question of whether the observed benefit associated with icosapent ethyl was entirely due to the study drug, or was, at least partially, contributed to by a negative effect from the mineral oil control (Orringer et al., 2019).

6.9 Baseline characteristics in the REDUCE-IT trial were well balanced between treatment

arms. The overall trial population had a mean age of 63 years. Patients in the secondary prevention population (representing 70.3% of the overall trial population) had a similar mean age, but included a higher proportion of male patients (78% versus 71%), a higher proportion with prior ASCVD (90% versus 69%), and a lower proportion with type 2 diabetes (41% versus 58%) compared to the overall trial population. Baseline lipid levels for the overall trial population and the secondary prevention population were similar. The median triglyceride level in the secondary prevention population was 2.47 mmol/L (<1.7 mmol/L: 10%; 1.7-2.3 mmol/L: 28%; > 2.3 mmol/L: 62%), the median LDL cholesterol level was 1.96 mmol/L, and the median HDL cholesterol level was 1.02 mmol/L.

6.10 Among patients in the secondary prevention population, the statin intensity was reported to be low for 4% of patients, moderate for 61% of patients, and high for 35% of patients, and 7% of patients were receiving treatment with ezetimibe. In general, the concomitant treatments used in the REDUCE-IT trial do not reflect current standard of care. Patients recruited for the trial were required to be on a stable dose of statin (rather than the maximum tolerated dose) and were encouraged to remain on the dose at enrolment during the trial. Use of PCSK9 inhibitors and fibrates was not permitted, and only a relatively small proportion of patients were receiving treatment with ezetimibe. Additionally, there may be wider use of diabetes treatments with evidence of cardiovascular benefit among patients in the proposed PBS population. The PSCR noted that when the trial was undertaken newer cardiovascular therapies, such as PCSK9 inhibitors, SGLT2 inhibitors and GLP-1 agonists, were not routinely available or used. The ESC noted that the concomitant treatments received by patients in the REDUCE-IT trial generally reflected the clinical guidelines in place when the trial was conducted. With regards to the dose of statins, the ESC noted that the maximum dose of statin was not required in the trial and that subgroup analyses of patients taking different doses of background statin therapy demonstrated that statin dose was not likely to be an effect modifier. The ESC noted that the low intensity statin subgroup did not meet statistical significance, but that there were low patient numbers in that analysis.

6.11 Many of the patients included in the trial with LDL levels of 1.8 to 2.6 mmol/L would be eligible for PBS treatment with a PCSK9 inhibitor (or patients may already be receiving treatment with a PCSK9 inhibitor). The PSCR stated that subgroup analyses of REDUCE-IT demonstrated a consistent effect of icosapent ethyl across all tertiles of LDL cholesterol (≤ 1.7 mg/dL vs. > 1.7 to ≤ 2.2 mg/dL vs. > 2.2 mg/dL; interaction p=0.1645).

6.12 There were limited data available to inform a comparison of the REDUCE-IT trial population with patients in the proposed PBS population. There may be differences between the clinical trial population and the proposed PBS population in underlying cardiovascular risk which affect the effectiveness of treatment with icosapent ethyl in clinical practice.

Comparative effectiveness

6.13 Table 4 presents the results for the primary 5-point MACE composite outcome (time to first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularisation, or unstable angina requiring hospitalisation) for the overall trial population and the secondary prevention population.

Table 4: Results for the primary 5-point MACE composite outcome in the REDUCE-IT trial

	ITT population		Secondary prevention population	
Parameter	**Icosapent ethyl N=4,089**	**Placebo N=4,090**	**Icosapent ethyl N=2,892**	**Placebo N=2,893**
Median follow-up, years	4.7	4.5	4.4	4.1
Composite outcome, n (%)	705 (17.2)	901 (22.0)	559 (19.3)	738 (25.5)
Hazard ratio (95% CI)	**0.75 (0.68, 0.83)**		**0.73 (0.65, 0.81)**	
Composite components [a]				
- CV death	137 (3.4)	149 (3.6)	101 (3.5)	113 (3.9)
- Nonfatal MI	205 (5.0)	280 (6.8)	168 (5.8)	234 (8.1)
- Nonfatal stroke	80 (2.0)	105 (2.6)	61 (2.1)	76 (2.6)
- Coronary revascularisation	189 (4.6)	244 (6.0)	147 (5.1)	201 (6.9)
- Hospitalisation for UA	94 (2.3)	123 (3.0)	82 (2.8)	114 (3.9)

Source: Table 2.5.1, p66 of the submission.

Abbreviations: CI, confidence interval; MI, myocardial infarction; NR, not reported; UA, unstable angina.

[a] Based on a patient's first post-randomisation occurrence of the event contributing to the composite outcome. The percentage reflects the number of patients experiencing an individual event divided by the total number of patients in the treatment arm (percentages included in the submission tables were based on the number of patients experiencing an individual event divided by the total number of events occurring in the treatment arm).

6.14 Treatment with icosapent ethyl in the overall trial population was associated with a statistically significant improvement in the time to first occurrence of the 5-point MACE composite outcome. Results for the secondary prevention subgroup were consistent with the results for the overall trial population.

6.15 Table 5 presents the results for the key secondary 3-point MACE composite outcome (time to first occurrence of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke) for the overall trial population and the secondary prevention population.

Table 5: Results for the key secondary 3-point MACE composite outcome in the REDUCE-IT trial

	ITT population		Secondary prevention population	
Parameter	**Icosapent ethyl N=4,089**	**Placebo N=4,090**	**Icosapent ethyl N=2,892**	**Placebo N=2,893**
Median follow-up, years	4.8	4.7	4.7	4.5
Composite outcome, n (%)	459 (11.2)	606 (14.8)	361 (12.5)	489 (16.9)
Hazard ratio (95% CI)	**0.74 (0.65, 0.83)**		**0.72 (0.63, 0.82)**	
Composite components [a]				
- Cardiovascular death, n (%)	149 (3.6)	167 (4.1)	109 (3.8)	131 (4.5)
- Nonfatal MI, n (%)	230 (5.6)	325 (7.9)	191 (6.6)	275 (9.5)
- Nonfatal stroke, n (%)	80 (2.0)	114 (2.8)	61 (2.1)	83 (2.9)

Source: Table 2.5.2, p68 of the submission; Table 14.2.1.2.1, p1 of Attachment 4 of the submission.

Abbreviations: CI, confidence interval; MI, myocardial infarction.

[a] Based on a patient's first post-randomisation occurrence of the event contributing to the composite outcome. The percentage reflects the number of patients experiencing an individual event divided by the total number of patients in the treatment arm (percentages included in the submission tables were based on the number of patients experiencing an individual event divided by the total number of events occurring in the treatment arm).

6.16 Treatment with icosapent ethyl in the overall trial population was associated with a statistically significant improvement in the time to first occurrence of the 3-point MACE composite outcome. The results for the secondary prevention subgroup were consistent with the results for the overall trial population.

6.17 Table 6 presents the results of secondary outcomes for the overall trial population and the secondary prevention population.

Table 6: Secondary outcomes in the REDUCE-IT trial

Parameter	ITT population			Secondary prevention population		
	Icosapent ethyl N=4,089	Placebo N=4,090	Hazard ratio (95% CI)	Icosapent ethyl N=2,892	Placebo N=2,893	Hazard ratio (95% CI)
CV death or nonfatal MI, n (%)	392 (9.6)	507 (12.4)	**0.75 (0.66, 0.86)**	310 (10.7)	416 (14.4)	**0.72 (0.63, 0.84)**
Fatal or nonfatal MI, n (%)	250 (6.1)	355 (8.7)	**0.69 (0.59, 0.81)**	208 (7.2)	303 (10.5)	**0.67 (0.56, 0.80)**
Urgent or emergent revascularisation, n (%)	216 (5.3)	321(7.8)	**0.65 (0.55, 0.78)**	178 (6.2)	277 (9.6)	**0.62 (0.52, 0.75)**
CV death, n (%)	174 (4.3)	213 (5.2)	**0.80 (0.66, 0.98)**	130 (4.5)	169 (5.8)	**0.76 (0.60, 0.95)**
Hospitalisation for unstable angina, n (%)	108 (2.6)	157 (3.8)	**0.68 (0.53, 0.87)**	93 (3.2)	143 (4.9)	**0.64 (0.49, 0.83)**
Fatal or nonfatal stroke, n (%)	98 (2.4)	134 (3.3)	**0.72 (0.56, 0.93)**	78 (2.7)	99 (3.4)	0.78 (0.58, 1.05)
Total mortality, nonfatal MI, or nonfatal stroke, n (%)	549 (13.4)	690 (16.9)	**0.77 (0.69, 0.86)**	434 (15.0)	551 (19.0)	**0.76 (0.67, 0.87)**
Total (all-cause) mortality, n (%)	274 (6.7)	310 (7.6)	0.87 (0.74, 1.02)	212 (7.3)	242 (8.4)	0.86, (0.72, 1.04)

Source: Table 2.5.3, p70 of the submission.

Abbreviations: CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.

Bolded results for the ITT population reflect statistically significant results. Bolded results for the secondary prevention population reflect nominal statistical significance (results for the secondary prevention population were not prespecified and were not adjusted for multiplicity).

6.18 In the overall trial population, treatment with icosapent ethyl was associated with a statistically significant reduction in cardiovascular death or nonfatal myocardial infarction; fatal or nonfatal myocardial infarction; urgent or emergent (non-elective) revascularisation; cardiovascular death; hospitalisation for unstable angina; fatal or nonfatal stroke; and the composite of total mortality, nonfatal myocardial infarction, or nonfatal stroke. There was no statistically significant difference for the outcome of all-cause mortality (the last secondary outcome in the hierarchical testing sequence), although the point estimate favoured icosapent ethyl. The results for the secondary prevention subgroup were generally consistent with the results for the ITT population. The results were considered exploratory and statistical testing was carried out at a nominal 5% level without adjustment for multiplicity.

6.19 Table 7 presents a summary of the change over time in lipid parameters in the REDUCE-IT trial for the overall trial population. Lipid results for the secondary prevention population were not included in the submission.

Table 7: Change over time in lipid levels in the REDUCE-IT trial

Parameter	Icosapent ethyl N=4,089			Placebo N=4,090			Between group difference (95% CI)		
	Median value	Absolute change	% change	Median value	Absolute change	% change	Absolute change	% change	p-value
Triglycerides (mg/dL)									
Baseline	216.5	-	-	216.0	-	-	-	-	-
Month 4	177.0	-37.5	-18.6%	221.0	5.5	2.7%	-45.5	-20.1%	<0.001
Year 1	175.0	-39.0	-18.3%	221.0	4.5	2.2%	-44.5	-19.7%	<0.001
Year 2	173.0	-38.5	-18.9%	220.0	4.3	2.1%	-43.8	-19.7%	<0.001
Year 3	167.0	-44.0	-21.7%	212.0	1.0	0.4%	-45.5	-20.3%	<0.001
Year 4	163.0	-42.5	-21.7%	200.0	-7.0	-3.7%	-38.0	-17.4%	<0.001
Year 5	158.0	-38.0	-20.0%	193.0	-3.0	-1.5%	-33.5	-16.7%	<0.001
Last visit	170.0	-45.0	-21.6%	202.0	-13.0	-6.5%	-32.0	-14.1%	<0.001
Non-HDL cholesterol (mg/dL)									
Baseline	118.0	-	-	118.5	-	-	-	-	-
Month 4	113.0	-4.5	-4.0%	128.0	9.5	8.2%	-14.3	-12.2%	<0.001
Year 1	113.0	-4.0	-3.6%	130.0	12.0	10.4%	-15.5	-13.1%	<0.001
Year 2	113.0	-3.5	-3.1%	129.0	11.5	9.8%	-14.5	-12.5%	<0.001
Year 3	112.0	-4.8	-4.2%	128.0	10.5	9.2%	-14.5	-12.4%	<0.001
Year 4	110.5	-5.0	-4.2%	126.0	9.5	8.1%	-14.0	-12.0%	<0.001
Year 5	109.0	-5.0	-4.4%	123.0	7.0	6.1%	-11.0	-9.9%	<0.001
Last visit	112.0	-5.0	-4.4%	124.0	6.0	5.1%	-10.0	-8.6%	<0.001
LDL cholesterol, Hopkins (mg/dL) [a]									
Baseline	85.8	-	-	86.7	-	-	-	-	-
Month 4	83.6	-1.6	-2.0%	93.7	7.3	8.7%	-8.7	-10.3%	<0.001
Year 1	85.3	-1.1	-1.2%	95.8	9.3	10.9%	-9.6	-11.4%	<0.001
Year 2	85.5	-0.1	-0.2%	96.1	9.5	11.4%	-9.4	-11.1%	<0.001
Year 3	84.6	-1.0	-1.2%	95.7	9.0	10.5%	-8.7	-10.4%	<0.001
Year 4	83.6	-0.5	-0.6%	94.7	8.8	10.1%	-8.9	-10.6%	<0.001
Year 5	82.2	-0.8	-0.7%	91.6	6.2	6.9%	-6.6	-8.0%	<0.001
Last visit	84.0	-1.0	-1.2%	92.1	5.7	6.5%	-6.2	-7.4%	<0.001
LDL cholesterol, derived (mg/dL)									
Baseline	74.0	-	-	76.0	-	-	-	-	-
Year 1	77.0	2.0	3.1%	84.0	7.0	10.2%	-5.0	-6.6%	<0.001
Last visit	77.0	2.0	3.1%	84.0	7.0	10.2%	-5.0	-6.6%	<0.001
HDL cholesterol (mg/dL)									
Baseline	40.0	-	-	40.0	-	-	-	-	-
Month 4	39.0	-1.0	-2.8%	42.0	2.0	4.7%	-3.0	-7.2%	<0.001
Year 1	39.0	-1.0	-2.6%	42.0	1.5	3.8%	-2.5	-6.3%	<0.001
Year 2	40.0	0.0	0.0%	42.0	1.5	4.2%	-2.0	-4.6%	<0.001
Year 3	40.0	0.0	0.0%	42.0	1.5	4.0%	-1.5	-3.8%	<0.001
Year 4	40.5	0.5	1.0%	43.0	2.0	4.8%	-1.5	-3.9%	<0.001
Year 5	41.0	0.0	0.0%	43.0	1.5	3.0%	-1.5	-3.0%	<0.001
Last visit	41.0	1.0	2.5%	42.0	2.0	5.7%	-1.0	-3.0%	<0.001

Source: Supplementary Table 4, p38 of the Bhatt *et al*. (2019) supplementary appendix.

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a] The Hopkins method of measurement is based on replacement of the fixed factor of 5 (used to estimate very low-density lipoprotein cholesterol) by an adjustable factor based on a patient's non-HDL cholesterol and triglyceride values.

6.20 At one year, treatment with icosapent ethyl was associated with a -19.7% difference in triglycerides, a -13.1% difference in non-HDL cholesterol, a -6.6% difference in derived LDL cholesterol, a -11.4% difference in Hopkins method LDL cholesterol, and

a -6.3% difference in HDL cholesterol compared to placebo. The differences in triglyceride, non-HDL cholesterol, and LDL cholesterol were generally maintained until Year 4. The results were considered exploratory and statistical testing was carried out at a nominal 5% level without adjustment for multiplicity. The difference in LDL cholesterol was almost completely due to increases in LDL cholesterol levels in the placebo arm, rather than a reduction in LDL cholesterol levels in the icosapent ethyl arm.

6.21 The ESC noted that there was uncertainty surrounding the relative magnitude of the benefit of icosapent ethyl, noting that patients in the placebo arm experienced increases in LDL cholesterol (Hopkins method) of between 8.7% and 11.4% over the first 4 years of the trial, whereas patients in the icosapent ethyl arm experienced decreases of up to 2.0% over the same period. Patients in the placebo arm also experienced increases in apolipoprotein B (7.8%) and high sensitivity C-reactive protein (32.3%) at Year 2. The PSCR noted that the percentage changes in LDL cholesterol correspond to approximately a 0.2 mmol/L difference and stated that this was a small difference in absolute terms. The PSCR also stated that other plausible reasons for the change in LDL cholesterol included the natural history of the disease and regression to the mean. The ESC noted that the potential harmful effect of mineral oil placebo in REDUCE-IT has been the subject of intense scrutiny. Similar effects on LDL cholesterol and high sensitivity C-reactive protein were not observed in a review of other clinical trials that have used mineral oil as placebo (Olshansky et al, 2020). Further, similar changes were not observed in the STRENGTH trial, which studied a very similar population to the REDUCE-IT trial and used a corn oil placebo. The possible effect of mineral oil on statin absorption has been postulated as one mechanism for the changes in the placebo group seen in REDUCE-IT. The ESC noted that some investigators have called for a new trial comparing icosapent ethyl with a bland placebo to definitively confirm a clinical benefit with icosapent ethyl and to characterise the magnitude of the cardiovascular effects (Bostrom et al, 2021). The pre-PBAC response stated that the STRENGTH trial studied a EPA/DHA mixture, which is less potent than icosapent ethyl, at lower total doses (2.2 g/day compared to 4 g/day) compared to the REDUCE-IT trial.

Comparative harms

6.22 Key adverse events occurring in the overall trial population of the REDUCE-IT trial are summarised in Table 8. Adverse event data for patients in the secondary prevention population of the REDUCE-IT trial were not included in the submission.

Table 8: Summary of adverse events in the REDUCE-IT trial

Trial ID	Icosapent ethyl N=4,089	Placebo N = 4,090
Mean treatment duration, years (SD)	3.71 (1.75)	3.56 (1.78)
Any treatment-emergent AE, n (%)	3,343 (81.8)	3,326 (81.3)
Severe AE, n (%)	805 (19.7)	816 (20.0)
Serious AE, n (%)	1,252 (30.6)	1,254 (30.7)
Treatment-related AE, n (%)	514 (12.6)	499 (12.2)
AE leading to treatment discontinuation n (%)	321 (7.9)	335 (8.2)
Serious AE leading to treatment discontinuation, n (%)	88 (2.2)	88 (2.2)
Serious AE leading to death, n (%)	94 (2.3)	102 (2.5)

Source: Table 12-2, p214; Table 12-3, pp216-217 of the REDUCE-IT clinical study report.
Abbreviations: AE, adverse event.

6.23 The incidence of adverse events was generally similar between treatment arms.

6.24 The most commonly reported treatment-emergent adverse events in the icosapent ethyl arm (>7%) were diarrhoea (9.0%), back pain (8.2%), hypertension (7.8%), nasopharyngitis (7.7%), arthralgia (7.7%), upper respiratory tract infection (7.6%) and bronchitis (7.5%). The most commonly reported treatment-related adverse events in the icosapent ethyl arm (>0.5%) were diarrhoea (2.7%), eructation (0.9%), flatulence (0.8%), nausea (0.8%) and arthralgia (0.6%). Treatment with icosapent ethyl was associated with a higher incidence (>1.0%) of peripheral oedema, constipation, and atrial fibrillation than the placebo arm.

6.25 The ESC noted that treatment with icosapent ethyl was associated with a higher incidence of bleeding-related disorders (11.8% versus 9.9%; p=0.0055) and a higher incidence of atrial fibrillation/flutter (7.7% versus 5.9%; p=0.0016) compared to placebo. Bleeding in patients on anti-thrombotic therapy and atrial fibrillation/flutter are important identified risks in the icosapent ethyl periodic benefit-risk evaluation report (PBRER). Further, it was noted that the EMA confirmed at its September 2023 meeting that atrial fibrillation was a common side effect of omega-3-acid esters and advised that they should be stopped if atrial fibrillation develops.[3]

Benefits/harms

6.26 A summary of the comparative benefits and harms for icosapent ethyl versus placebo is presented in Table 9.

[3] European Medicines Agency. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 25-28 September 2023: New safety information for Omega-3-acid ethyl esters. Available at: https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-25-28-september-2023

Table 9: Summary of comparative benefits and harms for icosapent ethyl and placebo

Event	Icosapent ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)
Benefits [a]			
Time to first occurrence of outcome [b]			
5-point MACE composite	559/2,892 (19.3)	738/2,893 (25.5)	0.73 (0.65, 0.81)
3-point MACE composite	361/2,892 (12.5)	489/2,893 (16.9)	0.72 (0.63, 0.82)
Cardiovascular death	130/2,892 (4.5)	169/2,893 (5.8)	0.76 (0.60, 0.95)
Fatal/nonfatal MI	208/2,892 (7.2)	303/2,893 (10.5)	0.67 (0.56, 0.80)
Fatal/nonfatal stroke	78/2,892 (2.7)	99/2,893 (3.4)	0.78 (0.58, 1.05)

Harms [c]						
Adverse event [d]	**Icosapent ethyl n/N**	**Placebo n/N**	**RR (95% CI)**	**Event rate/100 patients**		**RD (95% CI)**
				Icosapent ethyl	**Placebo**	
Atrial fibrillation	215/4,089	159/4,090	1.35 (1.11, 1.65)	5.3	3.9	0.01 (0.00, 0.02)
Bleeding-related disorders	482/4,089	404/4,090	1.19 (1.05, 1.35)	11.8	9.9	0.02 (0.01, 0.03)
Peripheral oedema	267/4,089	203/4,090	1.32 (1.10, 1.57)	6.5	5.0	0.02 (0.01, 0.03)

Source: Table 2.5.1, p66; Table 2.5.2, p68; Table 2.5.3, p70; Table 2.5.7, p76 of the submission.
HR = hazard ratio; PBO = placebo; RD = risk difference; RR = risk ratio.
[a] Based on the results for the secondary prevention population of the REDUCE-IT trial.
[b] Median follow-up 4.4 years and 4.1 years for icosapent ethyl and placebo for the 5-point MACE composite, respectively; 4.7 years and 4.5 years, respectively, for 3-point MACE composite; not reported for individual outcomes.
[c] Based on the results for the overall trial population of the REDUCE-IT trial.
[d] Based on a median follow-up of 4.9 years.

6.27 On the basis of direct evidence presented in the submission, for every 100 patients treated with icosapent ethyl in comparison with placebo over 4.9 years:

- Approximately 6 fewer patients will experience a major adverse cardiovascular event consisting of either cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularisation, or unstable angina requiring hospitalisation.
- Approximately 4 fewer patients will experience a major adverse cardiovascular event consisting of either cardiovascular death, nonfatal myocardial infarction or nonfatal stroke).
- Approximately 1 fewer patient will experience a death from cardiovascular causes.
- Approximately 3 fewer patients will experience a myocardial infarction (fatal or nonfatal).
- An additional patient will experience an episode of atrial fibrillation.
- An additional 2 patients will experience a bleeding-related adverse event.
- An additional 2 patients will experience an episode of peripheral oedema.

Clinical claim

6.28 The submission described icosapent ethyl as superior in terms of effectiveness, with an inferior but manageable safety profile, compared with placebo (as a proxy for standard of care).

6.29 The ESC considered that the therapeutic conclusion presented in the submission was uncertain, noting that the magnitude of the overall effect size of icosapent ethyl was unknown as the results of the REDUCE-IT trial may have been impacted by the use of the mineral oil placebo, which likely increased LDL cholesterol levels. A confirmatory trial using an alternative placebo may be required to confirm a clinical benefit of icosapent ethyl and to characterise the magnitude of cardiovascular benefit. The submission adjusts for the potential negative effect of the mineral oil placebo in the economic analysis by applying a 3% adjustment to cardiovascular event probabilities in the standard of care arm. The pre-PBAC response increased this adjustment to 7% (see paragraph 6.39).

6.30 The ESC noted that the following issues should also be considered:

- The treatments used in the REDUCE-IT trial were not consistent with current standard of care. Patients were not permitted to use PCSK9 inhibitors in the trial, optimisation of statin treatment was not required, and only a relatively small proportion of patients were using ezetimibe. Differences in use of other medications with the potential for lowering cardiovascular risk (such as SGLT2 inhibitors and GLP-1 agonists for the treatment of diabetes) may also potentially lower clinical benefits with icosapent ethyl in clinical practice. The PSCR noted that when the trial was undertaken a number of newer cardiovascular therapies, such as PCSK9 inhibitors, SGLT2 inhibitors and GLP-1 agonists, were not routinely available or prescribed.
- LDL treatment targets have reduced since the REDUCE-IT trial was conducted. The triglyceride-lowering effects of statins (dose optimised), ezetimibe and PCSK9 inhibitors may affect the proportion and risk profile of patients who will meet the proposed triglyceride and LDL cholesterol restriction criteria. The PSCR stated that subgroup analyses of REDUCE-IT demonstrated a consistent effect of icosapent ethyl across all tertiles of LDL cholesterol.
- The mechanism(s) of action for icosapent ethyl underlying the cardiovascular benefits is unclear but is unlikely to be related to the degree of triglyceride lowering. The uncertainty over the mechanism of action means that there is potential for overlap between the cardiovascular risk reduction associated with icosapent ethyl and other ASCVD treatments used to reduce cardiovascular risk (such as lipid-lowering therapies and diabetes treatments).
- Limited data were presented in the submission to allow comparison of PBS population characteristics with the patients in the REDUCE-IT trial. It is unclear

whether the cardiovascular risk among patients in the PBS population is the same as for patients in the REDUCE-IT trial.

6.31 The PBAC considered that the claim of superior comparative effectiveness was reasonable, but that the magnitude of the benefit was uncertain.

6.32 The PBAC agreed with ESC and considered that the claim of inferior but manageable safety appeared reasonable given the higher incidence of bleeding events and atrial fibrillation/flutter in the icosapent ethyl arm compared to the placebo arm of the REDUCE-IT trial.

Economic analysis

6.33 The submission presented a modelled economic evaluation comparing icosapent ethyl plus standard of care to standard of care, for the treatment of ASCVD with elevated triglyceride levels and adequately controlled LDL cholesterol. The economic evaluation was based on the results of the REDUCE-IT trial (using the placebo arm of the REDUCE-IT trial as a proxy for standard of care), with additional modelled data. The economic evaluation was presented as a cost-utility analysis.

Table 10: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Icosapent ethyl plus standard of care versus standard of care
Time horizon	25 years in the model base case versus a median follow-up of 2.9 years in the REDUCE-IT trial.
Outcomes	Life years; quality-adjusted life years.
Methods used to generate results	Markov cohort expected value analysis
Health states	Event free, post MI, post stroke, post MI and stroke, dead.
Cycle length	6 months
Transition probabilities	Event rates (nonfatal MI, nonfatal stroke, cardiovascular death, coronary revascularisation, hospitalisation for unstable angina) for each 6-month cycle over the initial 5 years were derived from a *post hoc* analysis of patient level data from the secondary prevention population of the REDUCE-IT trial. An adjustment of 3% was applied to cardiovascular events in the standard of care arm to reflect a potential negative impact of mineral oil (used as the placebo in the REDUCE-IT trial) on cardiovascular outcomes. The adjustment was increased to 7% in the pre-PBAC response. An age-related adjustment factor based on an analysis of AIHW prevalence data (acute coronary events, coronary heart disease deaths, stroke deaths, stroke events, coronary heart disease hospitalisation rates and atrial fibrillation hospitalisation rates) was applied to cardiovascular event and adverse event probabilities. Non-cardiovascular mortality was based on Australian life tables with adjustment for cardiovascular deaths using General Record of Incidence of Mortality (GRIM) data.
Extrapolation method	Event rates from 5 to 25 years were assumed to be the average 6-month probability of events over the initial 5 years in the secondary prevention population of the REDUCE-IT trial. Icosapent ethyl treatment persistence was based on extrapolated time to treatment discontinuation data for the icosapent ethyl arm of the REDUCE-IT trial.
Health related quality of life	Health state utilities sourced from a published economic model (Gao *et al*., 2019). Cardiovascular event disutilities sourced from a published economic model (Michaeli *et al*., 2022). Adverse event disutilities sourced from a published economic model (Ademi *et al*., 2021).
Costs	Drug costs: Icosapent ethyl drug cost based on the proposed DPMQ. Statin cost based on atorvastatin 20 mg DPMQ (Item 8214H). Health state costs: 'Event free' health state cost assumed to be nil. This was increased to $2,000 in the pre-PBAC response. 'Post MI' and 'post stroke' health state costs sourced from a published economic model (Gao *et al*., 2019). 'Post MI and stroke' cost assumed to be the same as for the 'post stroke' health state. Event costs: Cardiovascular event and cardiovascular death costs based on the NHCDC Public Hospitals Report, 2019–20 (AR-DRG version 10). Non-cardiovascular death cost assumed to be nil. Adverse event costs based on the NHCDC Public Hospitals Report, 2019–20 (AR-DRG version 10).

Source: Section 3, pp100-149 of the submission.

Abbreviations: AR-DRG, Australia refined diagnosis-related group; DPMQ, dispensed price for maximum quantity; MI, myocardial infarction; NHCDC, National Hospital Cost Data Collection.

6.34 In the model, all patients start in the 'event free' health state and can subsequently transition to the 'post myocardial infarction', 'post stroke', 'post myocardial infarction and stroke', and 'death' health states. It is unclear whether the model structure adequately captures the progressive nature of ASCVD, given that patients in the 'event free' health state already have established cardiovascular disease and may have already experienced a myocardial infarction or stroke. The ESC considered that the structure of the model was appropriate; however, the 'event free' health state should reflect the costs and utilities of being alive with ASCVD and managing established disease.

6.35 To align with the proposed PBS population with established ASCVD, the model was based on the results for the secondary prevention population of the REDUCE-IT trial. There may be differences between the clinical trial population and the proposed PBS population in underlying cardiovascular risk. Patients recruited for the trial were required to be on a stable dose of statin rather than the maximum tolerated dose, and were encouraged to remain on the dose at enrolment during the trial. Use of PCSK9 inhibitors and fibrates was not permitted, and only a relatively small proportion of patients were receiving treatment with ezetimibe. An uncertain proportion of the patients with LDL levels of 1.8 to 2.6 mmol/L would be eligible for PBS treatment with a PCSK9 inhibitor. Further, the ESC noted that the proportion of male patients in the secondary prevention population of the REDUCE-IT trial was 78.4%, and therefore potentially not reflective of the proposed PBS population and the underlying cardiovascular risk. The pre-PBAC response stated that subgroup analyses demonstrated that sex was not an effect modifier.

6.36 Patient level data for the secondary prevention population in the REDUCE-IT trial were used to estimate the probability of nonfatal myocardial infarction, nonfatal stroke, coronary revascularisation, hospitalisation for unstable angina and cardiovascular death. The submission model allowed patients who experienced an event (i.e., a myocardial infarction or stroke) in a given 6-month cycle to remain at risk of a further event in subsequent cycles (by including patients who had already experienced an event in the calculation of cardiovascular events/transition probabilities in subsequent cycles). The submission argued that this ensured that the economic model captured all clinically relevant events that occurred over the trial period. However, this assumption resulted in patients who had experienced an event being inappropriately included in the calculation of transitions in subsequent cycles (e.g., a patient who experienced a nonfatal myocardial infarction could be included in the calculation of events for the 'event free' and 'post stroke' health states in subsequent cycles). In the absence of individual patient data to allow tracking of individual patients, it may be more appropriate to censor patients at the time of the first event.

6.37 In the model base case, patients who discontinued icosapent ethyl treatment were censored from the calculation of transition probabilities. The submission stated that this was to align with the way the probabilities are used in the economic model. However, transition probabilities in the standard of care arm were derived with no censoring of patients who had discontinued placebo treatment. It may not be reasonable to adopt different approaches for the icosapent and standard of care arms, as there may be underlying reasons for treatment discontinuation that are associated with efficacy outcomes. The PSCR stated that applying the ITT data in the standard of care arm was appropriate as there was no need to differentiate this arm of the model for the purpose of effectiveness or costing. However, applying the ITT data in the icosapent ethyl arm was inappropriate in the context of the on and off treatment health states included in the model (e.g. the ITT risk already reflect treatment persistence from the trial (~50% at 4 years) and therefore also applying treatment

discontinuation risks an inappropriate double 'diluting' of the icosapent ethyl treatment effect). The ESC considered that it was not reasonable to adopt different approaches for the two arms, given that there may be underlying reasons for treatment discontinuation that are associated with efficacy outcomes. The ESC noted that the inclusion of censoring of discontinuing patients in both arms increased the ICER to $55,000 to < $75,000 per QALY, whereas removing them from both arms increased the ICER to $45,000 to < $55,000 - see Table 13. The ESC considered no censoring for discontinuation in either arm was more appropriate. The pre-PBAC response stated that it was not necessarily known which direction this bias will take (patients with lower CV risk overall may be more inclined to discontinue treatment for example which would mean this approach biased against icosapent ethyl); thus, the ESC approach was argued to systematically and inappropriately overestimate the rate of events in the icosapent ethyl arm of the model.

6.38 The probability of experiencing a cardiovascular event or a hospitalisation for atrial fibrillation was adjusted to account for age-related change in risk. Data published by the AIHW on the prevalence of acute coronary events (2020), coronary heart disease deaths (2019), stroke deaths (2019), stroke events (2020), coronary heart disease hospitalisation rates (2020-2021) and atrial fibrillation hospitalisation rates (2020-2021) were used to estimate the event risk relative to a trial period reference age of 68 years.

6.39 The submission stated that to account for any uncertainty around the potential impact of mineral oil in the placebo arm of REDUCE-IT, the effects of a 3% reduction in relative benefit of icosapent ethyl versus placebo were included in the base case of the economic model. The 3% value was selected based on the results of a Cox proportional hazards model, which was conducted based on LDL cholesterol outcomes at 1 year. Longer term lipid results indicated that the higher LDL cholesterol level in the placebo arm was maintained in subsequent years. It is unclear whether an assumed 3% reduction in relative treatment benefit adequately addresses the uncertainty around the use of mineral oil as the placebo in the REDUCE-IT trial. The ESC noted the study by Doi et al. 2021 which found that the effect of mineral oil on LDL cholesterol, triglycerides, and high sensitive C-reactive protein would be expected to increase ASCVD risk by 7%. Doi et al, 2021 also found that the expected between-group difference associated with the effects of icosapent ethyl on LDL cholesterol, triglycerides, and high sensitive C-reactive protein was 12%. However, the ESC noted that there were some potential limitations with the Doi et al. 2021 study including (i) differences in the baseline population characteristics between the cohort mimicking the REDUCE-IT trial and the REDUCE-IT trial, (ii) differences in concomitant treatments used and (iii) differences in the treatment settings (i.e. REDUCE-IT: RCT versus Doi: clinical practice). Further, the ESC noted that other HTA bodies applied larger adjustments for the negative effects of mineral oil (European Public Assessment Report (EPAR) notes that the negative effect of mineral oil would not be more than 10%). Noting the limitation with Doi et al. 2021, the ESC considered that sensitivity

analyses incorporating adjustments of 7% and 10% would be informative.

6.40 The pre-PBAC response accepted an adjustment of 7% to account for uncertainties related to the impact of the use of mineral oil as the placebo. Although the pre-PBAC suggested this adjustment was directly applied to the relative risk reduction in the trial, this is incorrect. The per cycle probability of each cardiovascular event in the standard of care arm of the model (nonfatal myocardial infarction, nonfatal stroke, cardiovascular death, hospitalisation for unstable angina, and coronary revascularisation) was multiplied by 0.97 (0.93 in the pre-PBAC response) to reflect the potential impact of mineral oil on cardiovascular outcomes. The adjustment was applied to the event probabilities for the placebo arm, which may not reflect a 3% (7%) difference in relative outcomes. It was noted that the 3% (7%) adjustment is applied equally to each of the individual outcomes. In the case a 5-point MACE outcome, each of the outcomes would have differing contributions to the endpoint depending on what occurs the earliest (i.e., with a greater contribution of non-fatal MI and coronary revascularisation).

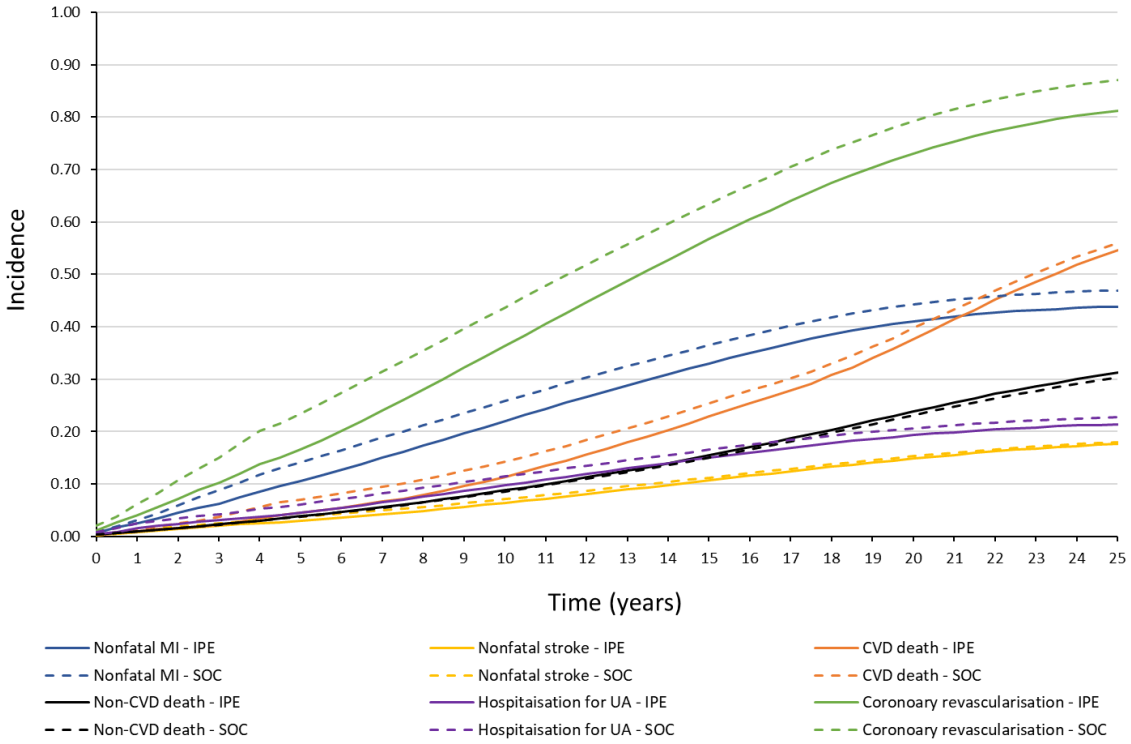
6.41 Health-related quality of life data was not collected in the REDUCE-IT trial. Health state utilities and disutilities in the model were sourced from published economic evaluations. The submission included a utility of 0.85 for the 'event free' state, 0.73 for the 'post myocardial infarction' state, 0.61 for the 'post stroke' state based on Gao et al. (2019), and assumed a utility of 0.61 (the lower of the 'post stroke' and 'post myocardial infarction' utilities) for the 'post myocardial infarction and stroke' health state. The assumed health state utility of 0.85 for patients in the event-free state may overestimate utility in this patient group, given the age of patients in the model, and given that all patients in the proposed PBS population have established ASCVD. No adjustment was applied to the utility over time to reflect higher levels of comorbidity associated with age/disease progression. The ESC noted that although the health state utilities were based on the Gao et al (2019) publication, Goa et al (2019) values were derived from utility values which were calculated using different mathematical metrics (EQ-5D and AQoL) and from papers from 2012 (Cobiac et al), 2006 (Hanmer et al) and 1993 (Fryback et al). The ESC was concerned that the utility values applied in the model did not reflect current values and that the mix of EQ-5D and AQoL to derive utility values and utility decrements contributed to the uncertainty.

6.42 Health state costs in the model were based on the costs included in a published economic analysis (Gao et al., 2019), and included $5,632 per 6-month cycle in the 'post myocardial infarction' health state, $3,972 in the 'post stroke' health state, and $5,632 in the 'post myocardial infarction and stoke' health state. The cost per cycle in the 'event free' health state was assumed to be nil. The ESC considered that the assumption of no cost for patients in the event free state was not reasonable, given that patients in the modelled population have established ASCVD and may have previously experienced a myocardial infarction or stroke. The ESC considered that the costs of managing established disease should have been included and noted that

Ademi et al, 2020[4] applied a cost of $5,229 for patients with who were 'alive with CVD'. The costs in the downstream health states (i.e. 'post MI', 'post stroke' and 'post MI and stroke') may also require adjustment to reflect the increasing disease burden. The pre-PBAC response provided a revised base case in which a cost of $2,000 was applied in the 'event-free' health state.

6.43 Figure 1 presents the proportion of patients experiencing cardiovascular events over time.

Figure 1: Proportion of patients experiencing cardiovascular events over time in the economic model

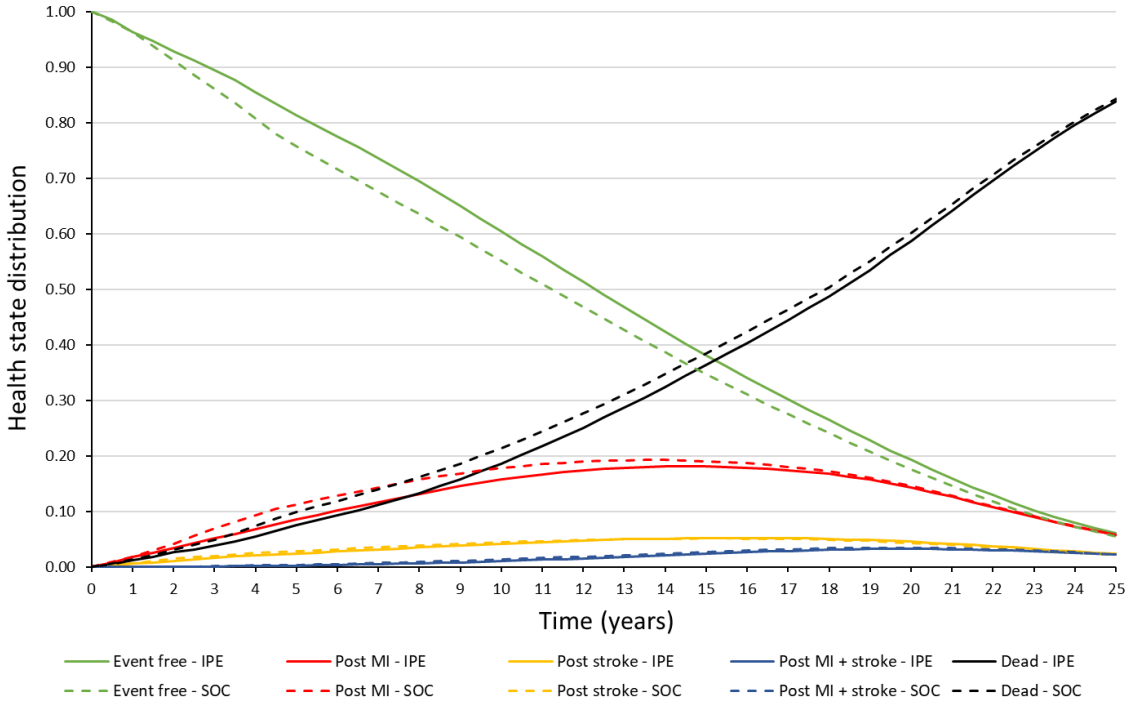


Source: Constructed using the Section 3 economic model Excel workbook.
Abbreviations: IPE, icosapent ethyl; MI, myocardial infarction; SOC, standard of care.

6.44 Figure 2 presents a Markov trace of the proportion of patients in each health state over time.

[4] Ademi Z, Ofori-Asenso R, Liew D, et al. The cost-effectiveness of icosapent ethyl in combination with statin therapy compared with statin alone for cardiovascular risk reduction. *European Journal of Preventive Cardiology*. 2020;0(0). doi:10.1177/2047487319896648

Figure 2: Proportion of patients in each health state over time



Source: Constructed using the Section 3 economic model Excel workbook.
Abbreviations: IPE, icosapent ethyl; MI, myocardial infarction; SOC, standard of care.

6.45 Patients in the icosapent ethyl plus standard of care arm spent a higher proportion of time in the event free health state compared to patients in the placebo plus standard of care arm.

6.46 The proportions of patients remaining alive at 5, 10, 15, 20 and 25 years were 92.6%, 81.4%, 63.7%, 41.3% and 16.2%, respectively, in the icosapent ethyl plus standard of care arm; and 90.1%, 78.6%, 61.6%, 39.9%, 15.6%, respectively in the placebo plus standard of care arm. The difference in the proportions of patients who had died at 4.5/5 years (2.3%/2.4%) was larger than the difference in total (all-cause) mortality reported for the secondary prevention cohort of the REDUCE-IT trial (1.1%), suggesting that the modelled results were not adequately calibrated to the trial results (noting that this comparison also included the 3% mineral oil adjustment for placebo arm event rates).

6.47 Key drivers of the economic model are summarised in Table 11.

Table 11: Key drivers of the model

Description	Method/Value	Impact
Cardiovascular event rates/ transition probabilities	In the model base case, patients who discontinued icosapent ethyl treatment were censored from the calculation of transition probabilities. This differed from the calculation of transition probabilities in the standard of care arm, which were derived with no censoring of patients who had discontinued placebo treatment. It may not be reasonable to adopt different approaches for the icosapent and standard of care arms, as there may be underlying reasons for treatment discontinuation that are associated with efficacy outcomes.	High, favours icosapent ethyl
Time horizon	The model base case incorporated a 25-year time horizon. There was a large amount of uncertainty associated with the extrapolation of the average event rates (and derived transition probabilities) in the REDUCE-IT trial from 5 years to 25 years.	Moderate, favours icosapent ethyl
Cardiovascular event risk	It is unclear whether the cardiovascular risk among the PBS population is the same as the secondary prevention population in the REDUCE-IT trial. In particular, ASCVD treatments included in the REDUCE-IT trial were not consistent with current standard of care.	Moderate, favours icosapent ethyl
Mineral oil adjustment	It is unclear whether the assumed 3% adjustment applied to the cardiovascular event probabilities in the standard of care arm adequately addresses the uncertainty around the use of mineral oil as the placebo in the REDUCE-IT trial	Moderate, favours icosapent ethyl
Health state costs	The base case of the model assumed no cost for patients in the event free state. This did not appear reasonable given that patients in the modelled population have established ASCVD and may have previously experienced an MI or stroke.	Moderate, favours icosapent ethyl

Source: Constructed during the evaluation based on the Section 3 economic model Excel workbook.
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; MI, myocardial infarction.

6.48 Results of the stepped economic evaluation are presented in Table 12. The result of the revised base case presented in the pre-PBAC response is also presented (adjustment for effects of mineral oil on the placebo arm increased from 3% to 7% and costs applied to the 'event free' health state increased from $0 to $2,000).

Table 12: Results of the stepped economic evaluation

Step and component	Icosapent ethyl	Standard of care	Increment
Step 1: Trial-based analysis over 5 years including drug costs			
Costs	$[redacted]	$794	[redacted]
Life years	4.349	4.304	0.044
Incremental cost/extra LY gained			[redacted][1]
Step 2: Modelled analysis over 25 years including drug costs			
Costs	$[redacted]	$2,109	[redacted]
Life years	11.734	11.436	0.297
Incremental cost/extra LY gained			[redacted][2]
Step 3: Modelled analysis over 25 years including drug costs, with inclusion of utilities			
Costs	$[redacted]	$2,109	[redacted]
QALYs	9.560	9.261	0.299
Incremental cost/extra QALY gained			[redacted][2]
Step 4: Modelled analysis over 25 years, including drug, health state and acute event costs, with inclusion of utilities			
Costs	$[redacted]	$32,157	[redacted]
QALYs	9.560	9.261	0.299
Incremental cost/extra QALY gained			[redacted][3]
Step 5: Modelled analysis over 25 years, including drug, health state and acute event costs, adjustment for age on cardiovascular risk, with inclusion of utilities			
Costs	$[redacted]	$32,466	[redacted]
QALYs	8.971	8.695	0.277
Incremental cost/extra QALY gained			[redacted][3]
Step 6: Modelled analysis over 25 years including drug, health state and acute event costs, adjustment for age on cardiovascular risk, adjustment for potential impact of mineral oil on placebo outcomes, with inclusion of utilities			
Costs	$[redacted]	$31,543	[redacted]
QALYs	9.039	8.779	0.260
Incremental cost/extra QALY gained (base case)			[redacted][2]
Pre-PBAC revised base case (7% adjustment for potential impact of mineral oil and $2,000 cost applied to the 'event free' health state)			
Costs	$[redacted]	$47,307	[redacted]
QALYs	9.130	8.893	0.237
Incremental cost/extra QALY gained (base case)			[redacted][2]

Source: Constructed using the Section 3 economic model Excel workbook.
Abbreviations: LY, life year; QALY, quality-adjusted life year.
The redacted values correspond to the following ranges:
[1] *$155,000 to < $255,000*
[2] *$25,000 to < $35,000*
[3] *$15,000 to < $25,000*

6.49 Based on the economic model, treatment with icosapent ethyl was associated with an incremental cost per QALY gained of $25,000 to < $35,000 compared to standard of care, or $25,000 to < $35,000, based on the pre-PBAC response.

6.50 The difference in total cost between treatment arms was primarily driven by the icosapent ethyl drug costs, which were partially offset by costs associated with the post myocardial infarction health state, and costs associated with coronary revascularisation. The difference in health outcomes between treatment arms was primarily driven by the higher number of life years accrued in the icosapent ethyl compared to the standard of care treatment arm, and by differences in time spent in the event-free health state.

6.51 In the model, 81% of incremental QALYs, 15% of the incremental drug costs, 73% of the incremental health state savings (post myocardial infarction, post stroke, post myocardial infarction and stroke), 104% of the incremental cardiovascular event savings (nonfatal myocardial infarction, nonfatal stroke, cardiovascular death, non-cardiovascular death, coronary revascularisation, hospitalisation for unstable angina), and 29% of the incremental adverse event costs (serious bleeding, hospitalisation for atrial fibrillation) were accrued in the extrapolated period beyond 5 years.

6.52 For every 1,000 patients treated with icosapent ethyl versus standard of care and followed up for 25 years, the economic evaluation (without discounting) estimated that there would be:

- An additional 44.6 years of life lived.
- An additional 43.4 years of quality-adjusted life lived.
- A reduction of 31 nonfatal myocardial infarctions, 3 nonfatal strokes, 15 cardiovascular deaths, 13 hospitalisations for unstable angina, 59 coronary revascularisations; and an additional 9 non-cardiovascular deaths.
- Additional drug costs of $[redacted] million and additional costs associated with the management of adverse events (serious bleeding, hospitalisation for atrial fibrillation) of $0.07 million.
- A reduction in health state costs of $2.0 million and a reduction in cardiovascular event costs (nonfatal myocardial infarction, nonfatal stroke, cardiovascular death, hospitalisation for unstable angina, coronary revascularisation procedures) of $1.4 million.

6.53 The results of key sensitivity analyses presented in the submission and conducted during the evaluation are summarised in Table 13.

Table 13: Sensitivity analyses

Analyses	Incremental cost ($)	Incremental QALY	ICER	% change
Base case	[redacted]	**0.260**	[redacted][1]	**-**
Discounting (base case: 5% costs and outcomes)				
0% costs and outcomes	[redacted]	0.434	[redacted][2]	-[redacted]
3.5% costs and outcomes	[redacted]	0.300	[redacted][2]	-[redacted]
Time horizon (base case: 25 years)				
15 years	[redacted]	0.211	[redacted][1]	[redacted]
20 years	[redacted]	0.246	[redacted][1]	[redacted]
37 years (to age 100)	[redacted]	0.264	[redacted][1]	-[redacted]
Population cardiovascular event risks (base case: derived from REDUCE-IT trial)				
Reduced by 20%	[redacted]	0.219	[redacted][1]	[redacted]
Reduced by 40%	[redacted]	0.174	[redacted][3]	[redacted]
Increased by 20%	[redacted]	0.297	[redacted][2]	-[redacted]
Increased by 40%	[redacted]	0.330	[redacted][2]	-[redacted]
Remove individual cardiovascular events from the model (base case: all included)				
Cardiovascular death	[redacted]	0.059	[redacted][4]	[redacted]
Hospitalisation for unstable angina	[redacted]	0.259	[redacted][1]	[redacted]
Coronary revascularisation	[redacted]	0.259	[redacted][1]	[redacted]
Nonfatal MI	[redacted]	0.235	[redacted][1]	[redacted]
Nonfatal stroke	[redacted]	0.252	[redacted][1]	[redacted]
Impact of mineral oil on event risks in placebo arm of REDUCE-IT (base case: 3%)				
0%	[redacted]	0.277	[redacted][2]	-[redacted]
5%	[redacted]	0.249	[redacted][1]	[redacted]
7% [A]	[redacted]	0.237	[redacted][1]	[redacted]
10% [B]	[redacted]	0.220	[redacted][1]	[redacted]
Duration of treatment effect (base case: 25 years; while on treatment)				
5 years	[redacted]	0.218	[redacted][1]	[redacted]
10 years	[redacted]	0.259	[redacted][1]	[redacted]
15 years	[redacted]	0.260	[redacted][1]	[redacted]
Transition probability calculation (base case: censoring for discontinuation applied to icosapent ethyl arm only; inclusive of recurrent events)				
Applied to neither arm; inclusive of recurrent events [C]	[redacted]	0.142	[redacted][5]	[redacted]
Applied to both arms; inclusive of recurrent events	[redacted]	0.094	[redacted][6]	[redacted]
Applied to icosapent ethyl arm only; first event only	[redacted]	0.251	[redacted][3]	[redacted]
Applied to both arms; first event only	[redacted]	0.083	[redacted][7]	[redacted]
Applied to icosapent ethyl arm only; first event only; event probabilities inclusive of recurrent events	[redacted]	0.2515	[redacted][1]	[redacted]
Non-cardiovascular death (base case: obtained from Australian life tables)				
Derived from REDUCE-IT trial	[redacted]	0.366	[redacted][2]	-[redacted]
Baseline age (base case: 63 years)				
60 years	[redacted]	0.273	[redacted][2]	-[redacted]
66 years	[redacted]	0.2501	[redacted][1]	[redacted]
69 years	[redacted]	0.2393	[redacted][1]	[redacted]
Health state utility values (base case: event free: 0.85; post MI: 0.73; post stroke: 0.61; post MI and stroke: 0.61)				
ICER model [a] - event free: 0.854; post MI: 0.704; post stroke: 0.650; post MI and stroke: 0.650 (assumption).	[redacted]	0.2655	[redacted][2]	-[redacted]
NICE model [b] - event free: 0.765; post MI: 0.669; post stroke:0.478; post-MI and stroke: 0.478 (assumption).	[redacted]	0.2352	[redacted][1]	[redacted]
Health state costs (base case: derived from Gao et al., 2019; $0 cost included for event free health state)				
Event free health state cost $2,000	[redacted]	0.260	[redacted][1]	[redacted]
Event free health state cost $5,229 [D]	[redacted]	0.260	[redacted][3]	[redacted]

Analyses	Incremental cost ($)	Incremental QALY	ICER	% change
Acute event costs (base case: derived from NHCDC Public Hospital Report – Round 24)				
Acute event costs doubled	[redacted]	0.260	[redacted][2]	-[redacted]
Reduced by 50%	[redacted]	0.260	[redacted][1]	[redacted]
Age-related cardiovascular risk adjustment (base case: included)				
Removed	[redacted]	0.2800	[redacted][2]	-[redacted]
Multivariate sensitivity analysis				
[A] Adjustment for effect of mineral oil = 7%; and [C] Censoring for discontinuation applied to neither arm	[redacted]	0.118	[redacted][6]	[redacted]
[B] Adjustment for effect of mineral oil = 10%; and [C] Censoring for discontinuation applied to neither arm	[redacted]	0.100	[redacted][6]	[redacted]
[A] Adjustment for effect of mineral oil = 7%; [C] Censoring for discontinuation applied to neither arm; and [D] Event free health state cost $5,229	[redacted]	0.098	[redacted][6]	[redacted]

Source: Constructed during the evaluation using the Section 3 economic model Excel workbook.
Abbreviations: MI, myocardial infarction.
[a] Institute for Clinical and Economic Review report (Additive Therapies for Cardiovascular Disease: Effectiveness and Value; 2019).
[b] National Institute for Health and Care Excellence ID3831 (2022).
The redacted values correspond to the following ranges:
[1] *$25,000 to < $35,000*
[2] *$15,000 to < $25,000*
[3] *$35,000 to < $45,000*
[4] *$95,000 to < $115,000*
[5] *$45,000 to < $55,000*
[6] *$55,000 to < $75,000*
[7] *$75,000 to < $95,000*

6.54 The modelled results were most sensitive to changes in the time horizon, changes in cardiovascular event risk, changes in health state costs, and the assumptions associated with the calculation of transition probabilities (i.e., inclusion of patients who discontinue treatment in placebo transition probability calculation; inclusion of first event only versus recurrent events).

6.55 The ESC considered that the multivariate sensitivity analysis that included a 7% adjustment for the effects of mineral oil, did not apply censoring for discontinuation to either arm and applied event free health state costs of $5,229 was more appropriate given the utilities remained unreliable. The ESC advised that a revised model and price reduction would be required to ensure icosapent ethyl was cost effective.

Drug cost/patient/year

6.56 Table 14 presents the drug costs for icosapent ethyl plus standard of care and standard of care included in the economic model and financial estimates.

Table 14: Drug cost per patient for icosapent ethyl and standard of care

	REDUCE-IT	Economic model		Financial estimates
Icosapent ethyl (plus standard of care)				
Treatment regimen	Icosapent ethyl: 2 g twice daily Statin: NR	Icosapent ethyl: 2 g twice daily Statin: atorvastatin 20 mg daily		Icosapent ethyl: 2 g twice daily Statin: Not included
Adherence	Icosapent ethyl: 97.5% Statin: NR	Icosapent ethyl: 97.5% Statin: 100%		Icosapent ethyl: 97.5%
Cost per year	-	Icosapent ethyl: $[redacted][a] Statin: $184.45[b]		Icosapent ethyl: $[redacted][c]
Persistence	Icosapent ethyl: Mean treatment duration 3.71 years Statin: Not reported	Icosapent ethyl: Year 1: 93%[d] Year 2: 85%[d] Year 3: 73%[d] Year 4: 59%[d] Year 5: 46%[d] Year 6: 33%[d]	Statin: Year 1: 100%[d] Year 2: 99%[d] Year 3: 97%[d] Year 4: 96%[d] Year 5: 95%[d] Year 6: 93%[d]	Icosapent ethyl: Not estimable [e]
Placebo (plus standard of care)				
Treatment regimen	Placebo: 2 capsules Statin: NR	Placebo: Not modelled Statin: Atorvastatin 20 mg daily		Placebo: Not included Statin: Not included
Adherence	Placebo: 100% Statin: NR	Placebo: Not included Statin: 100%		-
Cost per year	-	Placebo: Nil Statin: $184.45[b]		-
Persistence	Placebo: Mean treatment duration: 3.56 years Statin: NR	Not modelled		-

Source: Table 12-1, p213 of the REDUCE-IT trial clinical study report; Section 3 economic model Excel workbook; Section 4 financial impacts Excel workbook.

[a] Based on the proposed DPMQ of $[redacted] per pack of 120 capsules, assuming 12.18 packs per year multiplied by treatment adherence of 97.5%.

[b] Based on the DPMQ of $15.15 per pack of 30 atorvastatin 20 mg tablets, assuming 12.18 packs per year multiplied by treatment adherence of 100%.

[c] There was a small difference in the annual cost of icosapent ethyl between the economic model and the financial estimates due to the assumption of 365 versus 365.25 days per year.

[d] Proportion of patients on treatment at the midpoint of each year; inclusive of mortality in the model.

[e] The submission used a prevalence-based approach to derive the financial estimates and it was not possible to determine the proportion of patients discontinuing treatment each year.

Estimated PBS usage & financial implications

6.57 This submission was considered by DUSC.

6.58 Key sources of data used to derive the financial estimates are presented in Table 15.

Table 15: Key inputs for financial estimates

Data	Value	Source	Evaluator and DUSC comments
Eligible population			
ASCVD prevalence by age group (males)	18-44: 0.7% 45-54: 3.3% 55-64: 10.0% 65-74: 19.8% ≥75: 32.1%	Prevalence of self-reported heart, stroke and vascular disease among males in 2017-2018 (AIHW; 2023).	The AIHW dataset includes a broader range of cardiovascular conditions than the proposed population, which is limited to patients with atherosclerotic coronary artery disease, cerebrovascular disease and peripheral vascular disease, and therefore the assumed prevalence rates are likely to be overestimated. It is unclear whether the self-reported prevalence rates of cardiovascular disease accurately reflect the underlying prevalence of clinician-diagnosed cardiovascular disease. DUSC agreed with the commentary that this is likely an overestimate based on the inclusion of a broader range of conditions than the restriction and self-reporting likely overestimates clinician diagnosis of disease.
ASCVD prevalence by age group (females)	18-44: 1.2% 45-54: 2.6% 55-64: 7.9% 65-74: 12.2% ≥75: 20.3%	Prevalence of self-reported heart, stroke and vascular disease among females in 2017-2018 (AIHW; 2023).	
Australian male and female population by age cohort	-	ABS 3222.0 Series B.	-
Proportion of adults with ASCVD	2024: [redacted][1] 2025: [redacted][1] 2026: [redacted][1] 2027: [redacted][1] 2028: [redacted][1] 2029: [redacted][1]	Calculated. Prevalence of ASCVD by sex and age cohort multiplied by the corresponding ABS population according to sex and age cohort.	-
Australian population 18-100 years	2024: [redacted][2] 2025: [redacted][2] 2026: [redacted][2] 2027: [redacted][2] 2028: [redacted][2] 2029: [redacted][2]	ABS 3222.0 Series B. Forecast Australian population aged 18-100 years.	-
Age/sex standardised ASCVD prevalence	2024: 6.61% 2025: 6.66% 2026: 6.72% 2027: 6.77% 2028: 6.82% 2029: 6.86%	Calculated. The estimated number of patients with ASCVD was divided by the forecast Australian population aged 18-100 years.	-
Proportion on statin-based lipid lowering therapy	75.9%	Based on the proportion of patients receiving treatment with statin monotherapy or a statin in combination with ezetimibe in the 'CODE RED: Overturning Australia's cholesterol complacency' report (Baker Heart and Diabetes Institute; 2020). The sample was based on 107,664 individuals with a diagnosis of ASCVD, a subsequent lipid level, and a prescription for lipid-lowering therapy in the 12 months prior to the lipid level. If there	The submission's estimate was not adequately justified, given that the proposed PBS restriction requires patients to be on a maximum dose of statin. Among patients treated with a statin in the CODE RED report, 40,198 patients were on high intensity statin, 32,977 were on a moderate intensity statin and 1,530 were on low intensity statins. Potential limitations associated with the MedicineInsight dataset include the dependence on the accuracy and completeness of data recorded in the general practice clinical systems, incomplete or missing information if care of patients is provided outside of a participating MedicineInsight practice or in

Data	Value	Source	Evaluator and DUSC comments
		were multiple eligible LDL measurements during the follow-up period, the minimum LDL cholesterol result a patient achieved during their follow-up period was chosen as the representative LDL cholesterol measurement.	another health care setting (e.g., specialist or hospital), and the potential for double counting of patients if multiple participating general practitioners are consulted. DUSC considered this to be uncertain and likely overestimated as it is unclear how many of the patients in the CODE RED report were at their maximum tolerated statin dose. The Pre-Sub-Committee Response (PSCR) states that it is likely patients receiving statins for secondary prevention would be on the maximum tolerated dose due to these patients be considered high risk. However, DUSC noted that this could not be justified with the available data considering the uncertain overlap between statin 'intensity' as reported in the CODE RED report and 'max tolerated dose'.
Proportion achieving LDL cholesterol levels of 1.04-2.6 mmol/L	75.2%	CODE RED: Overturning Australia's cholesterol complacency. May 2020, Baker Heart and Diabetes Institute, Melbourne, Australia. (Carrington 2020). Calculated from Table 11 and Figure 8B.	The estimates related to the entire study cohort, which included patients who were not receiving statin treatment. The submission claimed that the results would be equally applicable to the statin-treated subpopulation. However, this claim may not be reasonable. As the results could have been from any time during the analysis period (i.e., 2010 to 2019), the lipid levels may not reflect the lipid levels in current clinical practice. Additionally, the study was largely undertaken prior to the availability of PCSK9 inhibitors. The availability of PCSK9 inhibitors may lead to higher numbers of patients with adequate LDL control. DUSC agreed with the commentary that this input is likely overestimated.
Proportion with triglyceride levels of 1.7-5.6 mmol/L	27.6%	Based on an analysis of data from the US National Health and Nutrition Examination Survey (NHANES). A total of 2,523 patients had qualifying triglyceride levels (≥150 mg/dL). The estimate was based on the proportion of patients who had a triglyceride level ≥150 mg/dL, were receiving statin therapy, and who had an LDL cholesterol level <100 mg/dL.	The applicability of the study result was unclear, as the study was based on a US population, had a relatively small sample size, was based on older survey data (2007-2014), and included patients with and without a diagnosis of ASCVD. Additionally, patients were not required to be receiving the maximum tolerated dose of a statin (which would provide additional triglyceride lowering effects). DUSC agreed with the commentary that this input is likely overestimated.
Treatment utilisation			
Uptake rate (prevalent patients)	Y1: [redacted]% Y2: [redacted]% Y3: [redacted]%: Y4: [redacted]% Y5: [redacted]% Y6: [redacted]%	Based on sponsor assumption.	The submission acknowledged the uncertainty associated with the uptake assumptions, and that the proposed uptake rates were possibly conservative, but argued that the proposed risk sharing arrangement would mitigate the financial risk to Government. DUSC considered that the uptake rates were likely underestimated given the claim of improved survival and a target population that is likely very familiar with over-the-counter fish oil products and would be inclined to switch.

Data	Value	Source	Evaluator and DUSC comments
Treatment persistence	Not estimable	The submission used a prevalence-based approach to derive the financial estimates.	Due to the prevalence-based approach, it was not possible to determine the proportion of patients discontinuing treatment each year. DUSC considered this not necessary in a prevalent approach.
Treatment adherence	97.5%	Based on the treatment adherence in the REDUCE-IT trial. Based on a mean number of capsules per patient per day of 3.9 (calculated as 3.9/4.0 = 0.975).	This is unlikely to be realised in practice given the high pill burden (4 x capsules per day) and known poor compliance with cholesterol treatments. DUSC agreed with the commentary that this input is likely overestimated however DUSC considered a treatment adherence rate similar to statins in the prevalent population would be appropriate (i.e. average prescriptions per person in a calendar year for statins) DUSC considered that reducing adherence to 80-85% would mean that the total number of scripts per year of icosapent ethyl would more closely resemble the total number of scripts per year of statin therapy for most people.
Costs			
Icosapent ethyl	$[redacted] per pack	Proposed DPMQ per pack of 120 icosapent ethyl 1 g capsules.	Application of 2023 fees and mark-ups resulted in a DPMQ of $[redacted].
Patient copayment	PBS: $12.93 RPBS: $5.91	Based on copayment split for fluvastatin (PBS Item 2863Q). Fluvastatin was selected on the basis that it is the only statin currently priced above the general co-payment level.	Fluvastatin may not be a reasonable proxy given the limited overall use in relation to statins.

Source: Section 4, pp150-162 of the submission; Section 4 financial implications Excel workbook.
Abbreviations: ABS, Australian Bureau of Statistics; AIHW, Australian Institute of Health and Welfare; ASCVD, atherosclerotic cardiovascular disease; DPMQ, dispensed price for maximum quantity; LDL, low-density lipoprotein.
Redacted values correspond to the following ranges:
[1] *1,000,000 to < 2,000,000*
[2] *> 10,000,000*

6.59 The estimated net cost to the PBS/RPBS of listing icosapent ethyl is presented in Table 16.

Table 16: Estimated use and financial implications

Patients treated with icosapent ethyl						
Australian population 18 to 100 years	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated ASCVD prevalence	6.61%	6.66%	6.72%	6.77%	6.82%	6.86%
Australian patients with ASCVD	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Proportion treated with maximum tolerated statin (75.9%)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Proportion with LDL cholesterol level 1.0-2.6 mmol/L (75.2%)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][4]
Proportion with triglyceride level 1.7-5.6 mmol/L (27.6%)	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
Icosapent ethyl uptake rate	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Total treated patients	[redacted][6]	[redacted][7]	[redacted][8]	[redacted][9]	[redacted][9]	[redacted][9]
Cost of icosapent ethyl to the PBS/RPBS						
Total scripts (11.86 per year)[1]	[redacted][5]	[redacted][10]	[redacted][11]	[redacted][12]	[redacted][12]	[redacted][12]
Cost to the PBS/RPBS ($204.71 per script)	[redacted][13]	[redacted][14]	[redacted][15]	[redacted][16]	[redacted][16]	[redacted][16]
Patient copayments[2]	[redacted][17]	[redacted][17]	[redacted][17]	[redacted][17]	[redacted][17]	[redacted][17]
Net cost to PBS/RPBS	[redacted][13]	[redacted][18]	[redacted][19]	[redacted][16]	[redacted][16]	[redacted][16]
Net cost to PBS/RPBS[3]	[redacted][13]	[redacted][18]	[redacted][19]	[redacted][16]	[redacted][16]	[redacted][16]

Source: Table 4.2.1 of the commentary (5.07.COM.101)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease.

[1] Based on 12.17 scripts per year multiplied by treatment adherence of 97.5%.

[2] Average PBS copayment of $12.93 and RPBS copayment of $5.91 based on dispensing data for Fluvastatin (PBS item 2863Q).

[3] Net cost to the PBS/RPBS recalculated during the evaluation using on July 2023 PBS markups.

The redacted values correspond to the following ranges:

[1] > 10,000,000
[2] 1,000,000 to < 2,000,000
[3] 800,000 to < 900,000
[4] 900,000 to < 1,000,000
[5] 200,000 to < 300,000
[6] 10,000 to < 20,000
[7] 20,000 to < 30,000
[8] 30,000 to < 40,000
[9] 40,000 to < 50,000
[10] 300,000 to < 400,000
[11] 400,000 to < 500,000
[12] 500,000 to < 600,000
[13] $40 million to < $50 million
[14] $70 million to < $80 million
[15] $90 million to < $100 million
[16] $100 million to < $200 million
[17] $0 to < $10 million
[18] $60 million to < $70 million
[19] $80 million to < $90 million

6.60 The estimated net cost to the PBS/RPBS was $40 million to < $50 million in Year 1, increasing to $100 million to < $200 million in Year 6, a total cost of $500 million to < $600 million over the first six years of listing. The estimated net cost to the PBS/RPBS (based on July 2023 PBS markups) was $40 million to < $50 million in Year 1, increasing to $100 million to < $200 million in Year 6, a total cost of $500 million to < $600 million over the first six years of listing.

6.61 The DUSC considered that overall, the financial implications were likely to be overestimated due to the following reasons:

- The epidemiological inputs used to derive the financial estimates (proportion of patients treated with a statin, the proportion of patients with an LDL cholesterol level of 1.0 to 2.6 mmol/L, and the proportion of patients with a triglyceride level of 1.7 to 5.6 mmol/L) were highly uncertain, lacked applicability to the proposed PBS population, and were relatively outdated. The estimates were generally based on the proportion of patients receiving treatment with a statin rather than the proportion of patients on the maximum tolerated dose of a statin. Changes in any of the epidemiological inputs had a large impact on the financial estimates.
- The estimated prevalence of ASCVD was based on a broader range of cardiovascular conditions than included in the proposed restriction and may overestimate the number of prevalent patients with ASCVD.
- The assumed treatment adherence of 97.5% is unlikely to be realised in practice given the high pill burden icosapent ethyl (4 x capsules per day), suboptimal compliance with statin therapy, and the large number of medications used in the management of ASCVD. When using a prevalent approach, a more appropriate calculation for prescriptions per person per year would be to use the average number of prescriptions per person per year for statin therapy in the current market (a prevalent market).

Quality Use of Medicines

6.62 The submission listed the following activities to support the quality use of medicines:

- Providing medical education materials and programs to familiarise general practitioners with the evidence-based prescribing of icosapent ethyl, and guidance regarding PBS restriction criteria for the secondary prevention of cardiovascular events.
- Developing medical education materials to assist clinicians in the identification of patients eligible for treatment, consistent with the proposed PBS restriction criteria.

6.63 Quality use of medicines issues identified include:

- Potentially reduced treatment benefit associated with icosapent ethyl among patients consuming a diet high in omega-3 fatty acids, or using omega-3 fatty acid supplement products. The DUSC noted that this should be highlighted to clinicians and patients.
- The icosapent ethyl product information states that it is not known whether patients with allergies to fish and/or shellfish are at increased risk of an allergic reaction to icosapent ethyl; and that icosapent ethyl should be used with caution in patients with known hypersensitivity to fish and/or shellfish. Additionally, the product information states that icosapent ethyl should not be used by patients who are allergic to soya or peanut.

- DUSC noted that no information was produced regarding degradation if icosapent ethyl were added to dose administration aids. DUSC considered that a portion of the target population would be using dose administration aids and it should be noted whether this form of administration would lead to a less efficacious medication similar to the impact of oxidation on fish oil preparations.
- DUSC noted the controversies surrounding fish farming which may present ecological and moral quandaries for some patients. DUSC considered that information on where and how fish are sourced in the manufacturing of icosapent ethyl may reduce these ethical concerns for patients.

Financial Management – Risk Sharing Arrangements

6.64 The submission proposed a Risk Sharing Arrangement with a tiered rebate structure to mitigate the financial risk to Government. Under the proposed arrangement, a rebate of [redacted]% would apply for expenditure between [redacted]% and [redacted]% of the estimated cost to government, and a [redacted]% rebate would apply to expenditure above [redacted]% of the estimated cost to Government.

6.65 Table 17 presents the risk-sharing arrangement caps proposed in the submission.

Table 17: Risk-sharing arrangement caps proposed in the submission

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Tier 1 cap[a]	[redacted][1]	[redacted][2]	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]
Tier 2 cap[b]	[redacted][2]	[redacted][5]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]

Source: Constructed using the Section 4 financial estimates Excel workbook.

[a] Based on the estimated cost to government.

[b] Based on the estimated cost to government multiplied by 150%.

The redacted values correspond to the following ranges:

[1] *$40 million to < $50 million*

[2] *$60 million to < $70 million*

[3] *$80 million to < $90 million*

[4] *$100 million to < $200 million*

[5] *$90 million to < $100 million*

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend icosapent ethyl for the treatment of patients with atherosclerotic cardiovascular disease (ASCVD) and elevated triglycerides. The PBAC considered that there was a low clinical need for icosapent ethyl given current therapies to treat patients with ASCVD are underutilised, and adding this option would complicate the treatment space at a substantial potential cost to Government. Furthermore, the PBAC considered the magnitude of benefit was uncertain given the mechanism of action of icosapent ethyl is inadequately understood, there are inconsistent trial results across studies of eicosapentaenoic acid (EPA) therapies and the negative impact of the mineral oil used in the placebo arm of the REDUCE-IT trial was not easily quantifiable. The PBAC considered that the revised incremental cost effectiveness ratio (ICER) presented in the pre-PBAC response was too high and

remained uncertain and that a substantial price reduction was required. In addition, the PBAC considered that the estimated utilisation and the financial impact were very high, and likely overestimated and, in the context of uncertain benefits and low clinical need, could not be justified. The PBAC advised that a Risk Sharing Arrangement (RSA) based on revised estimates and which consisted of expenditure caps beyond which 100% rebates would be required.

7.2 The primary reason for this outcome was the cost to Government presented in the submission.

7.3 The PBAC noted the sponsor hearing provided useful confirmation that the mechanism of action for icosapent ethyl was not easily defined. It was argued by the clinician that the impact of mineral oil on the placebo treatment effect was not likely to be substantial and that the 7% adjustment provided in the pre-PBAC response may be conservative.

7.4 The PBAC noted the consumer comments from four health professionals was supportive of icosapent ethyl being an available treatment option for lowering triglycerides. However, the PBAC considered that there was a low clinical need for icosapent ethyl for triglyceride lowering.

7.5 The PBAC noted that the proposed place in therapy, for the treatment of patients with ASCVD, a triglyceride level ≥ 1.7 mmol/L and < 5.6 mmol/L, and a low-density lipoprotein (LDL) cholesterol level of > 1.0 mmol/L and ≤ 2.6 mmol/L was consistent with the main clinical trial. However, the PBAC considered that the clinical need for a treatment targeting the lowering of triglycerides was low, given icosapent ethyl's mechanism of action works on multiple pathways, as noted in the sponsor hearing (see paragraph 6.1), and the ASCVD benefits of triglyceride lowering across fish oil studies is not conclusive (see paragraph 4.6). Furthermore, it was considered that the substantial financial cost to Government for this additional treatment option of uncertain value (see paragraph 7.9), which may be prescribed alongside other PBS-subsidised ASCVD treatments, was not justified.

7.6 The PBAC considered that placebo was the appropriate comparator.

7.7 The PBAC noted that the submission was based on the results of the secondary prevention cohort from the REDUCE-IT trial, a randomised controlled trial that compared icosapent ethyl to placebo.

7.8 The PBAC noted that icosapent ethyl was associated with a statistically significant improvement in the two key outcomes, the 5-point major cardiac event (MACE) outcome (HR = 0.73; 95% CI: 0.65, 0.81) and the 3-point MACE outcome (HR = 0.72; 95% CI: 0.63, 0.82), and all the secondary outcomes, with the exception of total (all cause) mortality in the secondary prevention cohort.

7.9 However, the PBAC noted the following:

- Over the first four years of the REDUCE-IT trial patients in the icosapent ethyl arm

experienced decreases of LDL cholesterol (Hopkins method) of between 0.2% and 2.0%, whereas those in the placebo arm had increases of LDL cholesterol of between 8.7% and 11.4%. Patients in the placebo arm also experienced increases in apolipoprotein B (7.8%) and high sensitivity C-reactive protein (32.3%) at Year 2. The PBAC noted that patients in the placebo arm received mineral oil and that the potential harmful effect of mineral oil placebo on LDL cholesterol levels in the REDUCE-IT trail has been the subject of intense scrutiny (see paragraphs 6.8 and 6.21);

- There was a long history of trials studying the effects of fish oils in ASCVD which have produced variable results (see paragraph 4.6) and that the benefits in terms of ASCVD were not conclusive;
- There was only modest support for icosapent ethyl in international treatment guidelines (see paragraph 4.7); and
- The mechanism of action of icosapent ethyl in reducing cardiovascular events was not completely understood, but it was thought to be largely independent of the triglyceride lowering effects (see paragraph 4.4 and 6.1). The PBAC considered that the uncertainty over the mechanism of action meant that there was potential for overlap between the cardiovascular risk reduction associated with icosapent ethyl and other ASCVD treatments used to reduce cardiovascular risk.

7.10 Thus, the PBAC considered that although icosapent ethyl was likely to be superior to placebo, the relative magnitude of the benefit was uncertain.

7.11 In terms of safety, the PBAC noted that although icosapent ethyl was associated with similar rates of adverse events as placebo, it was associated with a higher incidence of bleeding-related disorders and atrial fibrillation (see paragraph 6.25). Thus, the PBAC considered that the claim that icosapent ethyl had an inferior, yet manageable, safety profile compared to placebo was appropriate.

7.12 The PBAC considered that the base case ICER presented in the submission of $25,000 to < $35,000 per quality adjusted life year (QALY) gained ($25,000 to < $35,000 in the pre-PBAC response) was significantly underestimated and included a number of parameters favourable to icosapent ethyl. The PBAC noted that the base case:

- included a 3% adjustment to the cardiovascular events in the placebo arm to reflect the potential negative impact of the use of mineral oil. The PBAC noted that this was increased to 7% in the pre-PBAC response, based on the results of Doi et al 2021, and considered that the more conservative adjustment was appropriate;
- did not include costs of treatment in the 'event free' health state, although all patients had established ASCVD. The PBAC noted that a cost of $2,000 was arbitrarily applied in the pre-PBAC response but considered that the cost of $5,229 for patients 'alive with CVD' from Ademi et al, 2020 was more appropriate; and

- censored patients who discontinued icosapent ethyl treatment from the calculation of transition probabilities, which differed from the calculation in the placebo arm, which were derived with no censoring of patients who had discontinued placebo. The PBAC considered that the same approach should be applied in both arms and, noting that there may be underlying reasons for treatment discontinuation that were associated with efficacy outcomes, it would be appropriate that no censoring for discontinuation was applied in either arm.

7.13 The PBAC noted that if the changes above were applied to the economic model, the resultant ICER was $55,000 to < $75,000 per QALY gained, which is unacceptably high. To align with prior similar recommendations and accounting for uncertain magnitude of benefit, the PBAC considered that an acceptable ICER for icosapent ethyl would be $20,000 per QALY gained and advised that a significant price reduction would be required.

7.14 The PBAC noted DUSC advice that uptake rates were potentially underestimated (see Table 15). However, the PBAC considered in the context of the low need and uncertain value, that the utilisation and financial impact estimates were uncertain and were more likely to be overestimated. In this context, and based on further reasoning described below, it was considered a reduction in uptake was appropriate. Overall, the PBAC considered that revised estimates should:

- reduce the prevalence of ASCVD by 10% across all age groups for both males and females. The PBAC considered that this would account for the prevalence estimates used which included a broader range of conditions, such as oedema and heart failure, as compared to the proposed restriction;
- lower the proportion of patients with triglyceride levels of between 1.7 to 5.6 mmol/L from 27.6% to 10%. The PBAC considered that the study that this assumption was based on was not applicable to the Australian population as it was based on older data (from 2007-2014) from a US population, had a small sample size, and included patients with and without ASCVD. The PBAC also noted that elevated triglyceride levels could also be significantly reduced with appropriate dietary advice (such as reduction in alcohol intake and adoption of proven dietary interventions such as the Mediterranean diet);
- reduce the uptake rates by 25% across the 6 years of estimates which would better reflect prescribing fatigue and concerns regarding side effects (i.e., reduced from [redacted]% in Year 1 and [redacted]% in Year 6 to [redacted]% in Year 1 to [redacted]% in Year 6); and
- reduce the adherence rate from 97.5% to 80%, based on the known poor compliance with statin treatments and the high pill burden for icosapent ethyl (4 capsules per day).

7.15 The PBAC also advised that a RSA would be required which consisted of expenditure caps based on the revised financial estimates, including a lower price, beyond which 100% rebates would apply.

7.16 In terms of the proposed restriction, the PBAC noted that although the initial supply restriction required patients to have at least one of coronary heart disease, cerebrovascular disease or peripheral vascular disease, no diagnostic criteria for these conditions were included. The PBAC considered that it would be appropriate for the restriction to include specific diagnostic criteria for these conditions that aligned with the criteria outlined in the REDUCE-IT trial. Also, the PBAC considered that the requirement for treatment with a maximum tolerated dose of a high intensity statin was not necessary, given the mechanism of action for EPA is not consistent with statins and subgroup analyses from the REDUCE-IT trial demonstrated that background statin dose was not likely to be an effect modifier (see paragraph 6.10); subgroup analyses demonstrated a consistent effect of icosapent ethyl across all tertiles of LDL cholesterol (≤ 1.7 mg/dL vs. > 1.7 to ≤ 2.2 mg/dL vs. > 2.2 mg/dL; interaction p=0.1645) (see paragraph 6.11). However, the PBAC considered that the continuing restriction should state that patients must remain on statin therapy whilst receiving icosapent ethyl. The restriction should align with the clinical trial which required patients be on stable therapy with a statin (with or without ezetimibe). The PBAC advised that the other revisions outlined in Section 3 would also be required.

7.17 The PBAC considered the outstanding issues could be resolved in a simple resubmission for icosapent ethyl using the early re-entry pathway. If the sponsor accepts this pathway, the following changes would all be required to address these outstanding issues without requiring further re-evaluation:

- Revisions to the economic model as outlined in paragraphs 7.12 and 7.13;
- Revision to the utilisation and financial impact estimates as outlined in paragraph 7.14;
- Present a RSA as per paragraph 7.15; and
- A revised restriction as per paragraph 7.16.

The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the sponsor cannot address the issues as outlined above in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.

7.18 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in

relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

CSL Seqirus is disappointed by this decision, however we will work with the PBAC to ensure timely access for patients with elevated triglycerides and atherosclerotic cardiovascular disease (ASCVD) to reduce the risk of further CV outcomes.