

## 7.10 ICOSAPENT ETHYL, Capsule 1 g, Vazkepa<sup>®</sup>, SEQIRUS (AUSTRALIA) PTY LTD.

### 1 Purpose

- 1.1 The early re-entry resubmission 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 The resubmission was based on the PBAC decision to not recommend icosapent ethyl for this indication from November 2023. This resubmission proposed to address the issues raised by PBAC as summarised in Table 1 below.

**Table 1: Issues raised by PBAC from the November 2023 submission for icosapent ethyl**

Matter of concern	Response	Addressed?
Revisions to the restriction including: <ul style="list-style-type: none"> <li>• addition of specific diagnostic criteria for coronary heart disease, cerebrovascular disease and peripheral vascular disease that aligned with the criteria outlined in the REDUCE-IT trial;</li> <li>• removal of the requirement that patients must be receiving the maximum tolerated dose of a high intensity statin from the initial restriction;</li> <li>• the addition of criteria allowing treatment in patients with statin intolerance or who are contraindicated;</li> <li>• the addition to the continuing restriction that patients must remain on statin therapy whilst receiving icosapent ethyl (if not contraindicated or intolerant); and</li> <li>• the addition of a criterion preventing the co-administration of icosapent ethyl with other agents that lower triglycerides such as fibrates and niacin.</li> </ul>	The early re-entry resubmission: <ul style="list-style-type: none"> <li>• added the specific diagnostic criteria from the REDUCE-IT trial;</li> <li>• amended the initial restriction to state that patients must be treated with 'a stable' dose of a statin, rather than the maximum tolerated dose;</li> <li>• added criteria to allow treatment in patients with statin intolerance or who are contraindicated;</li> <li>• added a criterion to the continuing restriction that patients must remain on statin therapy; and</li> <li>• not addressed in the resubmission and no additional criterion preventing the co-administration of icosapent ethyl with other agents that lower triglycerides was proposed.</li> </ul>	Yes  Yes  Yes  Yes  No

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Matter of concern	Response	Addressed?
<p>Revisions to the economic model including:</p> <ul style="list-style-type: none"> <li>increasing the adjustment to the cardiovascular events in the placebo arm from 3% to 7% to better reflect the potential negative impact of the use of mineral oil (as proposed in the November 2023 pre-PBAC response);</li> <li>applying a cost of treatment in the 'event free' health state of \$5,229 (from Ademi 2020);</li> <li>applying no censoring for discontinuation to both the treatment and placebo arms; and</li> <li>a price reduction so that the ICER was \$<sup>2</sup> per QALY gained.</li> </ul>	<p>The early re-entry resubmission provided results of requested revisions, and a <sup>1</sup>% price reduction, resulting in an ICER of \$<sup>1</sup> per QALY gained. However, the base case specified by the resubmission included some alternative options for consideration that are less biased against icosapent ethyl:</p> <ul style="list-style-type: none"> <li>the effects of a 3% reduction are included in the base case supported by a number of concordant sources previously presented in November 2023;</li> <li>the event free health state cost was proposed to be set to be the same as the post stroke health state cost, \$3,972 per annum;</li> <li>the adherence to treatment proposed be reduced from 97.5% (3.9 capsules per day) to 80% (3.2 capsules per day); and</li> <li>reduced the DPMQ of icosapent ethyl by <sup>3</sup>% to result in an ICER of \$<sup>3</sup> per QALY gained</li> </ul>	Partially
<p>Revisions to the utilisation and financial impact estimations including:</p> <ul style="list-style-type: none"> <li>reducing the prevalence of ASCVD by 10% across all age groups for both males and females;</li> <li>lowering the proportion of patients with triglyceride levels of between 1.7 to 5.6 mmol/L from 27.6% to 10%;</li> <li>reducing the uptake rates by 25% across the 6 years of estimates; and</li> <li>reducing the adherence rate from 97.5% to 80%.</li> </ul>	<p>The early re-entry resubmission:</p> <ul style="list-style-type: none"> <li>reduced the prevalence of ASCVD by 10% for all patients;</li> <li>did not amend the proportion of patients with triglyceride levels of between 1.7 to 5.6 mmol/L;</li> <li>in recognition of retaining the previous proportion of patients meeting triglyceride levels, uptake rates reduced by between 31% and 46%; and</li> <li>reduced the adherence rate from 97.5% to 80%.</li> </ul>	<p>Yes</p> <p>No</p> <p>Yes</p> <p>Yes</p>
<p>Provision of a RSA which consisted of expenditure caps based on the revised financial estimates and lower price, beyond with <sup>3</sup>% rebates would apply.</p>	<p>The early re-entry resubmission presented a two-tiered RSA – one that aligned with the revised financial estimates and a second at <sup>3</sup>% higher than the revised estimates. Expenditure between the two tiers was to be rebated at <sup>3</sup>%, with all expenditure above the second tier rebated at <sup>3</sup>%</p>	Partially

Source: compiled from the November 2023 icosapent ethyl minutes and the March 2024 early re-entry resubmission  
ASCVD = atherosclerotic cardiovascular disease; DPMQ = dispensed price for maximum quantity; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year; RSA = risk-sharing arrangement

The redacted values correspond to the following ranges:

<sup>1</sup> \$45,000 to < \$55,000

<sup>2</sup> \$15,000 to < \$25,000

<sup>3</sup> \$25,000 to < \$35,000

## 2 Background

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 ( $\geq 1.7$  mmol/L) and

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

2.2 The PICO from the previous submission is presented below.

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Table 2: Key components of the clinical issues addressed in the resubmission

Component	Description
Population	Adult patients with atherosclerotic cardiovascular disease (ASCVD), a triglyceride level $\geq 1.7$ mmol/L and $< 5.6$ mmol/L, and an LDL cholesterol level $> 1.0$ mmol/L and $\leq 2.6$ 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.

LDL = low-density lipoprotein; MI = myocardial infarction.

For more detail on PBAC's view, see section 5 PBAC outcome.

### 3 Requested listing

3.1 The resubmission presented a revised proposed restriction based on the suggestions in the November 2023 PBAC minutes.

3.2 Secretariat additions are in italics and deletions in strikethrough.

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

Concept ID	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> 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.
	Episodicity: blank
	Severity: blank
	Condition: blank
	Indication: Established atherosclerotic cardiovascular disease with hypertriglyceridaemia
	Treatment Phase: 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 <del>heart</del> artery disease, (ii) cerebrovascular <i>or carotid</i> disease, (iii) peripheral <del>vascular</del> arterial disease
	AND
	Clinical criteria
	Patient must be treated with 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

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	Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have LDL cholesterol level between 1.0 mmol/L and 2.6 mmol/L
	<b>AND</b>
	<b>Clinical criteria</b>
	Patient must have fasting triglyceride level between 1.7 mmol/L and 5.6 mmol/L
	<b>Prescribing instructions:</b> 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.
	<b>Prescribing instructions:</b> 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.
	<b>Prescribing instructions:</b> Atherosclerotic cardiovascular disease is defined as: (i) Documented coronary artery disease (CAD); one or more of the following primary criteria must have been satisfied: <ul style="list-style-type: none"> <li>• Documented multi-vessel CAD (≥50% stenosis in at least two major epicardial coronary arteries, with or without antecedent revascularisation).</li> <li>• Documented prior MI.</li> <li>• Hospitalisation for high-risk non-ST-segment elevation acute coronary syndrome, with objective evidence of ischemia: ST-segment deviation or biomarker positivity.</li> </ul> (ii) Documented cerebrovascular or carotid disease; one of the following primary criteria must have been satisfied: <ul style="list-style-type: none"> <li>• Documented prior ischemic stroke.</li> <li>• Symptomatic carotid artery disease with ≥50% carotid arterial stenosis.</li> <li>• Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis per angiography or duplex ultrasound.</li> <li>• History of carotid revascularisation (catheter-based or surgical).</li> </ul> (iii) Documented peripheral arterial disease; one or more of the following primary criteria must have been satisfied: <ul style="list-style-type: none"> <li>• Ankle brachial index (ABI) &lt;0.9 with symptoms of intermittent claudication.</li> <li>• History of aorto-iliac or peripheral arterial intervention (catheter-based or surgical).</li> </ul>
<b>Concept ID</b>	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
	<b>Indication:</b> Established atherosclerotic cardiovascular disease with hypertriglyceridaemia
	<b>Treatment Phase:</b> Continuing treatment
	<b>Clinical criteria:</b>
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	<b>AND</b>

	<b>Clinical criteria:</b>
	The treatment must be in combination with dietary therapy and exercise
	<b>AND</b>
	<b>Clinical criteria:</b>
	Treatment must be co-administered with a HMG CoA reductase inhibitor (statin), unless the patient is contraindicated to statins or has developed statin related adverse events necessitating withdrawal of statin treatment

- 3.3 The proposed population is a subgroup of the TGA indicated population and is based on secondary prevention.
- 3.4 The PBAC was asked to consider whether the proposed STREAMLINED Authority level, consistent with the restrictions for ezetimibe, is appropriate. Evolocumab and alirocumab have a telephone/online Authority level for initial supply.
- 3.5 The proposed indication is ‘Established atherosclerotic cardiovascular disease with hypertriglyceridaemia’. The PBAC was asked to advise whether this indication is appropriate, or whether it would be more reasonable to have an indication of ‘Hypertriglyceridaemia’ with a clinical criterion stating ‘Patient must have established atherosclerotic cardiovascular disease’.
- 3.6 The resubmission provided specific diagnostic criteria for coronary heart disease, cerebrovascular disease and peripheral arterial disease based on the inclusion criteria of the REDUCE-IT trial. Based on this addition, the Secretariat has amended the clinical criterion in the initial treatment restriction as follows:
- Patient must have at least one of (i) coronary heart artery disease, (ii) cerebrovascular or carotid disease, (iii) peripheral vascular arterial disease
- 3.7 The resubmission did not include a criterion precluding use in combination with other agents that lower triglycerides such as fibrates and niacin (paragraph 3.3, icosapent ethyl minutes, November 2023). The PBAC was asked to advise if a criterion should be added to the proposed restrictions.

*For more detail on PBAC’s view, see section 5 PBAC outcome.*

## 4 Consideration of the evidence

### **Sponsor hearing**

- 4.1 There was no hearing for this item.

### **Consumer comments**

- 4.2 In addition to comments previously received, the PBAC noted and welcomed the input from an additional organisation via the Consumer Comments facility on the PBS website. The PBAC noted the comments from hearts4heart which considered that the listing of a therapeutic treatment to manage triglyceride associated residual cardiovascular risk would be a welcome addition to the options available which focus on other risk factors associated with ASCVD. As previously noted by PBAC in

November 2023, the mechanism of action was suggested to involve multiple pathways, with potential beneficial effects on cardiovascular endpoints, as seen in the REDUCE-IT trial 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 (paragraph 6.1, icosapent ethyl Public Summary Document [PSD], November 2023).

### ***Clinical claim***

- 4.3 The November 2023 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).
- 4.4 The PBAC considered that although icosapent ethyl was likely to be superior to placebo, the relative magnitude of the benefit was uncertain (paragraph 7.10, icosapent ethyl PSD, November 2023) for the reasons outlined in paragraph 7.9 of the November 2023 icosapent ethyl PSD.
- 4.5 In terms of safety, the PBAC considered that the claim that icosapent ethyl had an inferior, yet manageable, safety profile compared to placebo was appropriate, noting 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 (paragraph 7.11, icosapent ethyl PSD, November 2023).
- 4.6 The PBAC consideration of the comparative clinical effectiveness and safety remain unchanged from November 2023.

### ***Economic analysis***

- 4.7 In November 2023, the PBAC considered that the base case ICER presented in the submission (\$25,000 to < \$35,000 per QALY) was significantly underestimated and included a number of parameters favourable to icosapent ethyl (paragraph 7.12, icosapent ethyl minutes, November 2023). The PBAC suggested three changes to the model which increased the ICER to \$55,000 to < \$75,000 per QALY:
  - Increasing the 3% adjustment to the cardiovascular events in the placebo arm to 7% to better reflect the potential negative impact of the use of mineral oil;
  - Including costs of \$5,229 per year for treatment of patients in the ‘event free’ health state, as they had established ASCVD; and
  - Applying no censoring for patients who discontinue icosapent ethyl treatment, so that the same approach was applied in both arms.
- 4.8 The PBAC considered that if the above changes were made to the model then, to align with similar recommendations and to account for the uncertain magnitude of benefit, the price of icosapent ethyl should be reduced to result in an ICER of \$15,000 to < \$25,000 per QALY (paragraph 7.13, icosapent ethyl minutes, November 2023).

4.9 As noted in Table 1, the resubmission presented the three suggested changes to the model and proposed a 1% reduction to the DPMQ of icosapent ethyl (from \$1 to \$0.99). These changes resulted in an ICER of \$45,000 to < \$55,000 per QALY; see Table 3.

**Table 3: Results of the economic model incorporating the changes requested by PBAC in November 2023**

	Incremental costs (\$)	Incremental QALYs	ICER
November 2023 submission base case		0.2601	1
<b>PBAC's requested revisions</b>			
Increase mineral oil adjustment from 3% to 7%		0.237	1
+ Include 'event free' health state costs of \$5,229		0.237	2
+ Apply no censoring to patients who discontinue treatment		0.118	3
+ Revise DPMQ to \$0.99		0.118	4

Source: Table 3, p7 of the early re-entry resubmission and Vazkepa Economic model

DPMQ = dispensed price for maximum quantity; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year

The redacted values correspond to the following ranges:

<sup>1</sup> \$25,000 to < \$35,000

<sup>2</sup> \$35,000 to < \$45,000

<sup>3</sup> \$55,000 to < \$75,000

<sup>4</sup> \$45,000 to < \$55,000

4.10 The resubmission acknowledged that the proposed ICER of \$45,000 to < \$55,000 per QALY was higher than the \$15,000 to < \$25,000 per QALY requested by the PBAC in November 2023, but argued that each of the requested changes biased against icosapent ethyl as follows:

- The mineral oil adjustment of 7% far exceeded what could be explained by the relatively small increases in LDL (low density lipoprotein) cholesterol observed in the REDUCT-IT trial and was not consistent with the clinical evidence. Additionally, the resubmission stated that the large meta-regression found that the difference in the rate of major coronary events attributable to the effects of mineral oil on LDL cholesterol levels in the placebo arm at five years would be a little over 1% (Silverman, 2016).
- The application of a cost of \$5,229 per year to patients in the event free health state assumed that there were almost no long-term cost consequences of preventing cardiovascular events in patients who have already had an event. Further, for patients that have a stroke, the result will be cost saving as they will move into a health state with costs of \$3,972 per year.
- As the intention to treat (ITT) treatment effect includes data from up to 50% of patients who discontinued treatment with icosapent ethyl but is applied to a health state before patients discontinue, assuming no censoring means that the model is accruing the cost of icosapent ethyl for those patients who have discontinued treatment.

4.11 Therefore, the resubmission provided an alternate revised base case in which:

- the use of ITT data for the icosapent ethyl transition probabilities was maintained. However, to account for level of discontinuation in the data and expected in practice, it was proposed that the adherence to treatment be reduced from 97.5%

(3.9 capsules per day) to 80% (3.2 capsules per day). This assumption brings the utilisation of icosapent ethyl in the economic model into alignment with utilisation in the financial impact estimations requested by PBAC and which form the basis of the proposed RSA.

- the adjustment to account for any uncertainty around the potential impact of mineral oil in the placebo arm of REDUCE-IT was reduced back to 3%. This resubmission stated that this reflected the maximum theoretical size of the impact of mineral oil on cardiovascular outcomes. The resubmission stated that the use of 3% was supported by a number of concordant sources, described in more detail in the November 2023 submission.
- the event free health state cost was reduced from \$5,229 per year to be the same as the post stroke health state cost of \$3,972 per year. This meant that for patients experiencing a stroke the model would no longer result in cost savings when moving from an event free state to having a stroke.

4.12 The alternate inputs resulted in a revised base case of \$25,000 to < \$35,000 per QALY, as outlined in Table 4.

**Table 4: Results of the economic model incorporating the Sponsor's alternate changes**

	Incremental costs (\$)	Incremental QALYs	ICER
November 2023 submission base case		0.260	1
<b>Sponsor's proposed revisions</b>			
No mineral oil adjustment		0.260	1
+ Include 'event free' health state costs of \$3,972		0.260	1
+ Apply no censoring to patients who discontinue treatment		0.142	2
+ Reduce adherence to treatment to 80%		0.142	3
+ Revise DPMQ to \$153.63		0.142	1
<b>Sensitivity analysis</b>			
Sponsor's alternate base case + 7% mineral oil adjustment		0.118	3

Source: Table 4, p9 of the early re-entry resubmission and Vazkepa Economic model

DPMQ = dispensed price for maximum quantity; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year

The redacted values correspond to the following ranges:

<sup>1</sup> \$25,000 to < \$35,000

<sup>2</sup> \$55,000 to < \$75,000

<sup>3</sup> \$35,000 to < \$45,000

4.13 The resubmission again acknowledged that the alternate ICER of \$25,000 to < \$35,000 per QALY was higher than the \$15,000 to < \$25,000 per QALY requested by the PBAC in November 2023, but stated that the ICER accounted for the uncertain magnitude of benefit when compared to the July 2022 recommendation of evolocumab in the secondary prevention of ASCVD; see Table 5. It was acknowledged this comparison was relatively superficial, but it was argued in the resubmission that this validation showed that the transformation of the magnitude of benefit in the trial data to the magnitude of benefit in the modelled results was substantially more conservative for icosapent ethyl than an otherwise very similar model recently considered by PBAC.

**Table 5: Comparison of outcomes between the Sponsor’s proposed model and the July 2022 evolocumab model**

	Icosapent ethyl	SoC	Increment	Evolocumab	SoC	Increment	Magnitude of benefit for icosapent ethyl relative to evolocumab
Non-fatal MI	0.4332	0.4682	-0.0350	0.7028	0.8289	-0.1261	72% lower
Non-fatal stroke	0.1733	0.1782	-0.0049	0.2682	0.3163	-0.0481	90% lower
CV death	0.5398	0.5468	-0.0070	0.522	0.588	-0.066	89% lower
LYs (undiscounted)	16.6757	16.4686	0.2071	16.4	15.7	0.67	69% lower
QALYs (discounted)	13.4322	13.1956	0.2366	8.279	7.983	0.296	20% lower

Source: Table 6, p11 of the early re-entry resubmission

CV = cardiovascular; LY = life year; MI = myocardial infarction; QALY = quality adjusted life year; SoC = standard of care.

### **Estimated PBS usage and financial implications**

4.14 The resubmission acknowledged that the main reason for the PBAC’s decision not to recommend icosapent ethyl in November 2023 was the total cost to government, which was estimated to be approximately \$500 million to < \$600 million over the first 6 years of listing. The PBAC suggested four changes to the financial estimates:

- Reducing the prevalence of ASCVD by 10% across all age groups for both male and female patients, as the estimates used in the submission included a broader range of conditions (e.g., oedema and heart failure) as compared to the proposed restriction;
- Lowering 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);
- Reducing 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 8% in Year 1 and 20% in Year 6 to 6% in Year 1 to 15% in Year 6); and
- Reducing 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).

4.15 As noted in Table 1, the resubmission reduced the prevalence of ASCVD by 10% and reduced the adherence rate from 97.5% to 80% as requested by the PBAC.

4.16 The resubmission did not lower the proportion of patients with triglyceride levels of between 1.7 and 5.6 mmol/L from 27.6% to 10%. The resubmission considered that the requested reduction was overstated, particularly as the US study that provided the estimate was not small (it had nearly 3,000 patients) and as it was considered unlikely that a Mediterranean diet would be efficacious and sustained in a population who should have already attempted lifestyle modification before beginning treatment

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with statins and other cardiovascular risk reduction medications. The PBAC advised the proportion of patients with ASCVD on statins with triglycerides in the range of 1.7-5.6 mmol/L could reasonably be considered as midway between what the submission assumed and what the PBAC requested ((27.6% + 10%) / 2 = 18.8%).

4.17 Noting that the 27.6% may be an overestimate in the Australian setting, the resubmission instead decreased the uptake rates of icosapent ethyl by greater than the requested 25% to between 31% and 46%. The PBAC advised more conservative estimates of uptake were required in order to establish an acceptable basis for financial caps, starting at 4.3% in Year 1 and increasing 1.14% per year to reach 10% in Year 6.

4.18 Table 6 presents a comparison of the utilisation inputs.

**Table 6: Comparison of utilisation inputs from November 2023 to March 2024**

Data	November 2023 value	March 2024 value	PBAC value
Age/sex standardised ASCVD prevalence	Year 1: 6.61% Year 2: 6.66% Year 3: 6.72% Year 4: 6.77% Year 5: 6.82% Year 6: 6.86%	Year 1: 5.95% Year 2: 6.00% Year 3: 6.05% Year 4: 6.10% Year 5: 6.14% Year 6: 6.18%	No change
% with triglyceride levels of 1.7-5.6 mmol/L	27.6%	27.6%	18.8%
Uptake rate (prevalent patients)	Year 1: 8.0% Year 2: 12.8% Year 3: 16.0%: Year 4: 18.4% Year 5: 19.6% Year 6: 20.0%	Year 1: 4.3% Year 2: 7.0% Year 3: 9.6%: Year 4: 12.0% Year 5: 13.5% Year 6: 15.0%	Year 1: 4.3% Year 2: 5.44% Year 3: 6.58%: Year 4: 7.72% Year 5: 8.86% Year 6: 10.0%
Treatment adherence (Scripts per patient)	97.5% (11.26)	80% (9.73)	No change
Icosapent ethyl DPMQ	\$ per pack	\$ per pack	No change

Source: Table 8, p13 of the early re-entry resubmission; Vazkepa Section 4 workbook Post PBAC minutes and Table 15, pp34-37 of the icosapent ethyl minutes, November 2023

ASCVD = atherosclerotic cardiovascular disease; DPMQ = dispensed price for maximum quantity

4.19 Table 7 presents the revised financial impact and provides a comparison with the November 2023 results.

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Table 7: Estimated utilisation and financial impact

	2024	2025	2026	2027	2028	2029
Australian population 18 to 100 years	1	1	1	1	1	1
Estimated ASCVD prevalence	5.95%	6.00%	6.05%	6.10%	6.14%	6.18%
Australian patients with ASCVD	2	2	2	2	2	2
Proportion treated with maximum tolerated statin (75.9%)	3	3	2	2	2	2
Proportion with LDL cholesterol level 1.0-2.6 mmol/L (75.2%)	4	4	4	4	4	5
Proportion with triglyceride level 1.7-5.6 mmol/L (27.6%)	6	6	6	6	6	6
Icosapent ethyl uptake rate	4.3%	7.0%	9.6%	12.0%	13.5%	15.0%
Total treated patients	7	7	8	8	8	9
<b>Cost of icosapent ethyl to the PBS/RPBS</b>						
Total scripts (9.73 per year) <sup>1</sup>	10	11	11	6	6	12
Cost to the PBS/RPBS (DPMQ = \$ )	13	14	15	15	16	17
Patient co-payments (\$12.77) <sup>2</sup>	18	18	18	18	18	18
<b>Net cost to PBS/RPBS</b>	13	13	14	15	16	16
<b>Net cost to PBS/RPBS - PBAC</b>	18	13	13	13	13	14
<b>November 2023 estimates</b>						
<b>Patients treated with icosapent ethyl</b>						
Australian population 18 to 100 years	1	1	1	1	1	1
Estimated ASCVD prevalence	6.61%	6.66%	6.72%	6.77%	6.82%	6.86%
Australian patients with ASCVD	2	2	2	2	2	2
Proportion treated with maximum tolerated statin (75.9%)	2	2	2	2	2	2
Proportion with LDL cholesterol level 1.0-2.6 mmol/L (75.2%)	5	5	5	5	5	3
Proportion with triglyceride level 1.7-5.6 mmol/L (27.6%)	6	6	6	6	6	6
Icosapent ethyl uptake rate	8.0%	12.8%	16.0%	18.4%	19.6%	20.0%
Total treated patients	7	8	9	19	19	19
<b>Cost of icosapent ethyl to the PBS/RPBS</b>						
Total scripts (11.86 per year) <sup>1</sup>	6	12	20	21	21	21
Cost to the PBS/RPBS (DPMQ = \$ )	16	22	23	24	24	24
Patient co-payments (\$12.77) <sup>2</sup>	18	18	18	18	18	18
<b>Net cost to PBS/RPBS</b>	16	25	26	24	24	24

Source: Table 8, p13 of the early re-entry resubmission, Vazkepa Section 4 workbook Post PBAC minutes and Table 16, p38 of the icosapent ethyl minutes, November 2023

ASCVD = atherosclerotic cardiovascular disease; DPMQ = dispensed price for maximum quantity; LDL = low density lipoprotein; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

<sup>1</sup> Based on 12.17 scripts per year multiplied by treatment adherence of 80%.

<sup>2</sup> Average PBS copayment of \$12.93 and RPBS copayment of \$5.91 based on dispensing data for Fluvastatin (PBS item 2863Q).

The redacted values correspond to the following ranges:

<sup>1</sup> > 10,000,000

<sup>2</sup> 1,000,000 to < 2,000,000

<sup>3</sup> 900,000 to < 1,000,000

<sup>4</sup> 700,000 to < 800,000

<sup>5</sup> 800,000 to < 900,000

<sup>6</sup> 200,000 to < 300,000

<sup>7</sup> 10,000 to < 20,000

<sup>8</sup> 20,000 to < 30,000

<sup>9</sup> 30,000 to < 40,000

<sup>10</sup> 80,000 to < 90,000

<sup>11</sup> 100,000 to < 200,000

<sup>12</sup> 300,000 to < 400,000

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<sup>13</sup> \$10 million to < \$20 million

<sup>14</sup> \$20 million to < \$30 million

<sup>15</sup> \$30 million to < \$40 million

<sup>16</sup> \$40 million to < \$50 million

<sup>17</sup> \$50 million to < \$60 million

<sup>18</sup> \$0 to < \$10 million

<sup>19</sup> 40,000 to < 50,000

<sup>20</sup> 400,000 to < 500,000

<sup>21</sup> 500,000 to < 600,000

<sup>22</sup> \$70 million to < \$80 million

<sup>23</sup> \$90 million to < \$100 million

<sup>24</sup> \$100 million to < \$200 million

<sup>25</sup> \$60 million to < \$70 million

<sup>26</sup> \$80 million to < \$90 million

4.20 The resubmission's revised estimated net cost to the PBS/RPBS was \$10 million to < \$20 million in Year 1, increasing to \$40 million to < \$50 million in Year 6 and totalling \$100 million to < \$200 million over the first 6 years of listing. Based on the PBAC revisions, the net cost to the PBS/RPBS was \$0 to < \$10 million in Year 1, increasing to \$20 million to < \$30 million in Year 6 and totalling an estimated \$80 million to < \$90 million over the first 6 years of listing. The November 2023 submission estimated a total cost of \$500 million to < \$600 million over the first 6 years of listing.

### **Financial management – Risk Sharing Arrangements**

4.21 In November 2023, the PBAC advised that an RSA would be required which consisted of expenditure caps based on the revised financial estimates, including a lower price, beyond which  $\frac{1}{2}$ % rebates would apply (paragraph 7.15, icosapent ethyl minutes, November 2023).

4.22 The resubmission proposed a two-tiered RSA in which a rebate of  $\frac{1}{2}$ % would apply for expenditure between  $\frac{1}{2}$ % and  $\frac{1}{2}$ % of the estimated cost to the PBS/RPBS, and a  $\frac{1}{2}$ % rebate would apply to expenditure above  $\frac{1}{2}$ % of the estimated cost to the PBS/RPBS; see Table 8.

4.23 The estimated net cost to the PBS/RPBS was \$100 million to < \$200 million over the first 5 years of listing. If usage exceeds Tier 2 of the proposed RSA, the maximum PBS/RPBS expenditure over the 5 years of the proposed RSA would be \$100 million to < \$200 million.

**Table 8: Proposed RSA expenditure caps**

	2024	2025	2026	2027	2028	Total over 5 years
Tier 1 expenditure cap	1	1	2	3	4	5
Tier 2 expenditure cap <sup>1</sup>	1	2	3	4	6	5
█% rebate for expenditure between Tiers 1 and 2	7	7	7	7	7	7
<b>Maximum PBS/RPBS expenditure</b>	1	2	2	3	4	5

Source: Table 9, p14 of the early re-entry resubmission

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

<sup>1</sup> Tier 1 expenditure cap x █%

The redacted values correspond to the following ranges:

<sup>1</sup> \$10 million to < \$20 million

<sup>2</sup> \$20 million to < \$30 million

<sup>3</sup> \$30 million to < \$40 million

<sup>4</sup> \$40 million to < \$50 million

<sup>5</sup> \$100 million to < \$200 million

<sup>6</sup> \$60 million to < \$70 million

<sup>7</sup> net cost saving

For more detail on PBAC’s view, see section 5 PBAC outcome.

## 5 PBAC Outcome

- 5.1 The PBAC recommended the listing of icosapent ethyl, on the basis that it should be available as a General Schedule Authority Required (STREAMLINED) listing for the treatment of patients with atherosclerotic cardiovascular disease (ASCVD) and elevated triglycerides. The PBAC was satisfied that icosapent ethyl provides, for some patients, a significant improvement in efficacy over standard care of care (consisting of dietary modification, lifestyle interventions, and concomitant optimisation of LDL cholesterol lowering using a statin-based therapeutic regimen). The PBAC acknowledged the proposals to address the substantive outstanding issues identified in November 2023 in this early re-entry resubmission, and considered the revised price offer and amendments to the economic model were sufficient if further containment of the overall budget impact was achieved.
- 5.2 The PBAC recalled it had previously noted that based on results of the secondary prevention cohort from the REDUCE-IT trial, 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.
- 5.3 However, the PBAC had also 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 trial has been the subject of intense scrutiny;

- There was a long history of trials studying the effects of fish oils in ASCVD which have produced variable results and that the benefits in terms of ASCVD were not conclusive;
- There was only modest support for icosapent ethyl in international treatment guidelines; 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. 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.

5.4 Thus, the PBAC considered that although icosapent ethyl was likely to be superior to placebo, the relative magnitude of the benefit was uncertain (paragraphs 7.8 to 7.10, icosapent ethyl PSD, November 2023).

5.5 The PBAC recalled it had specified the following revisions to the economic model would be required to achieve an acceptable incremental cost-effectiveness ratio (ICER):

- increasing the adjustment to the cardiovascular events in the placebo arm from 3% to 7% to better reflect the potential negative impact of the use of mineral oil (as proposed in the November 2023 pre-PBAC response);
- applying a cost of treatment in the ‘event free’ health state of \$5,229 (from Ademi 2020);
- applying no censoring for discontinuation to both the treatment and placebo arms; and
- a price reduction so that the ICER was \$15,000 to < \$25,000 per QALY gained (paragraphs 7.12 and 7.13, icosapent ethyl PSD, November 2023).

5.6 The PBAC noted the resubmission offered a [REDACTED] % price reduction, which together with the above amendments resulted in an ICER of \$45,000 to < \$55,000 per QALY gained. The resubmission proposed alternative scenarios with more favourable outcomes, which resulted in an ICER of \$25,000 to < \$35,000 per QALY gained (see Table 1).

5.7 The PBAC was amenable to some flexibility in the ICER value it had previously stipulated. However, given the early re-entry pathway proposed by PBAC stipulated more stringent model parameters to counter the uncertain magnitude of benefit, the PBAC was minded to only accept the resubmission’s revised alternative base case ICER

in the context of more conservative financial estimates and an appropriate Risk Sharing Arrangement (RSA).

5.8 The PBAC recalled it had previously stipulated the changes to the financial estimates would be required as follows:

- 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 8% in Year 1 and 20% in Year 6 to 6% in Year 1 to 15% 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) (paragraphs 7.12 and 7.13, icosapent ethyl PSD, November 2023).

5.9 The PBAC noted the revised financial estimates in the resubmission included reduced prevalence of ASCVD and a greater reduction in uptake than was required. However, the resubmission retained the same proportion of patients with high triglyceride levels. The PBAC recalled it had considered the cost to Government to be a key reason for its initial decision to not recommend, and while the proposed revisions did significantly reduce the potential budget impact, the listing remained very high cost over 6 years in an already heavily funded market. In the context of accepting a favourable and higher than requested ICER, the PBAC did not consider the estimated financial implications were a sound basis for establishing caps for an RSA. The PBAC has advised the following changes would need to be implemented to provide acceptable alternative estimates (see paragraphs 4.16 and 4.17):

- the proportion of ASCVD on statins with TGs 1.7-5.6mmol/L should be reduced from 27.6% to 18.8%.
- uptake starting at 4.3% in Year 1 and increasing 1.14% per year to reach 10% in Year 6. The PBAC felt that uptake in this population, who are already taking multiple medications, would be lower than projected by the sponsor.

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- 5.10 The PBAC considered the lower financial estimates based on these additional changes should form the basis of a single tier RSA with a 1% rebate for expenditure above the caps (see Table 7 for the Net cost to PBS/RPBS - PBAC).
- 5.11 The PBAC considered the revisions to the requested restriction were acceptable. Specifically, the PBAC agreed with:
- the resubmission proposed Streamlined authority level, given step-wise progression through LDL-c lowering therapies was not required;
  - the resubmission proposed indication of ‘Established atherosclerotic cardiovascular disease with hypertriglyceridaemia’ rather than ‘Hypertriglyceridaemia’ given, as argued in the pre-PBAC response, that although triglycerides were used to characterize the at-risk patients within REDUCE-IT, the outcomes in the trial were cardiovascular outcomes;
  - not excluding the use of fibrates/niacin in the restriction. As argued in the pre-PBAC response, these therapies are not used for reducing cardiovascular risk but rather for reducing the risk of pancreatitis or diabetic retinopathy; and
  - the Secretariat amended clinical criterion in the initial treatment restriction as follows:  

Patient must have at least one of (i) coronary heart artery disease, (ii) cerebrovascular or carotid disease, (iii) peripheral vascular arterial disease.
- 5.12 The PBAC recommended that icosapent ethyl should not be treated as interchangeable on an individual patient basis with any other drugs, according to s101(3BA) of the National Health Act.
- 5.13 The PBAC advised that icosapent ethyl is not suitable for prescribing by nurse practitioners.
- 5.14 Icosapent ethyl should not be exempt from the Early Supply Rule as it currently applies to similar drugs for chronic conditions.
- 5.15 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for icosapent ethyl:
- a) The treatment may be expected to provide a clinically relevant improvement in efficacy, over alternative therapies, but the magnitude of benefit is uncertain;
  - b) The treatment is not expected to address a high and urgent unmet clinical need because there are alternative treatment options for ASCVD;
  - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

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5.16 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 6 Recommended listing

6.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item number	Max. qty packs	Max. qty units	№. of Rpts	Available brands
ICOSAPENT ETHYL					
Icosapent ethyl 998 mg capsule, 120	NEW	1	120	5	Vazkepa
<b>Concept ID)</b>	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)				
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners				
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED)				
	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.				
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.				
	<b>Episodicity:</b> blank				
	<b>Severity:</b> blank				
	<b>Condition:</b> blank				
	<b>Indication:</b> Established atherosclerotic cardiovascular disease with hypertriglyceridaemia				
	<b>Treatment Phase:</b> Initial treatment				
	<b>Clinical criteria:</b>				
	The treatment must be in combination with dietary therapy and exercise				
	<b>AND</b>				
	<b>Clinical criteria:</b>				
	Patient must have at least one of (i) coronary artery disease, (ii) cerebrovascular or carotid disease, (iii) peripheral arterial disease				
	<b>AND</b>				
	<b>Clinical criteria</b>				
	Patient must be treated with 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				
	<b>AND</b>				
	<b>Clinical criteria:</b>				
	Patient must have LDL cholesterol level between 1.0 mmol/L and 2.6 mmol/L				
	<b>AND</b>				
	<b>Clinical criteria</b>				
	Patient must have fasting triglyceride level between 1.7 mmol/L and 5.6 mmol/L				
	<b>Prescribing instructions:</b>				

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	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.
	<p><b>Prescribing instructions:</b> A clinically important product-related adverse event is defined as follows:</p> <p>(i) Severe myalgia (muscle symptoms without creatine kinase elevation) which is proven to be temporally associated with statin treatment; or</p> <p>(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</p> <p>(iii) Unexplained, persistent elevations of serum transaminases (greater than 3 times the upper limit of normal) during treatment with a statin.</p>
	<p><b>Prescribing instructions:</b> Atherosclerotic cardiovascular disease is defined as:</p> <p>(i) Documented coronary artery disease (CAD); one or more of the following primary criteria must have been satisfied:</p> <ul style="list-style-type: none"> <li>• Documented multi-vessel CAD (≥50% stenosis in at least two major epicardial coronary arteries, with or without antecedent revascularisation).</li> <li>• Documented prior MI.</li> <li>• Hospitalisation for high-risk non-ST-segment elevation acute coronary syndrome, with objective evidence of ischemia: ST-segment deviation or biomarker positivity.</li> </ul> <p>(ii) Documented cerebrovascular or carotid disease; one of the following primary criteria must have been satisfied:</p> <ul style="list-style-type: none"> <li>• Documented prior ischemic stroke.</li> <li>• Symptomatic carotid artery disease with ≥50% carotid arterial stenosis.</li> <li>• Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis per angiography or duplex ultrasound.</li> <li>• History of carotid revascularisation (catheter-based or surgical).</li> </ul> <p>(iii) Documented peripheral arterial disease; one or more of the following primary criteria must have been satisfied:</p> <ul style="list-style-type: none"> <li>• Ankle brachial index (ABI) &lt;0.9 with symptoms of intermittent claudication.</li> <li>• History of aorto-iliac or peripheral arterial intervention (catheter-based or surgical).</li> </ul>

<b>Concept ID</b>	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
	<b>Indication:</b> Established atherosclerotic cardiovascular disease with hypertriglyceridaemia
	<b>Treatment Phase:</b> Continuing treatment
	<b>Clinical criteria:</b>
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be in combination with dietary therapy and exercise
	<b>AND</b>
	<b>Clinical criteria:</b>
	Treatment must be co-administered with a HMG CoA reductase inhibitor (statin), unless the patient is contraindicated to statins or has developed statin related adverse events necessitating withdrawal of statin treatment

***These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.***

## **7 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.

## **8 Sponsor's Comment**

CSL welcomes the decision to recommend Vazkepa on the PBS as it addresses an important unmet clinical need to reduce the cardiovascular risk in patients with established cardiovascular disease and elevated triglycerides. However, CSL believes that the clinical need will be higher than the estimated uptake of 10% of eligible patients at Year 6, and we will continue to work with the PBAC to facilitate a reasonable and sustainable level of uptake.