

**7.09 ALIROCUMAB,
Injection 75 mg in 1 mL single dose pre-filled pen,
Injection 150 mg in 1 mL single dose pre-filled pen,
Praluent[®],
Sanofi-Aventis Australia Pty Ltd**

1 Purpose of Application

- 1.1 The minor resubmission sought an Authority Required listing for alirocumab for the treatment of non-familial hypercholesterolaemia (non-FH) in patients with atherosclerotic cardiovascular disease (ASCVD) and additional high-risk factors.
- 1.2 Listing was requested on the basis of a cost-minimisation analysis versus evolocumab, in the same population as that for which evolocumab was recommended in November 2019, and at no additional net cost to the Pharmaceutical Benefits Scheme (PBS).
- 1.3 The minor resubmission made the following changes from the previous March 2019 major submission:
 - a revised restriction based on the PBAC’s July 2019 advice for evolocumab for the non-FH population.
 - a revised economic analysis to reflect the requested listing of alirocumab on a cost-minimisation basis versus evolocumab.
 - a request to join the Risk Sharing Arrangement (RSA) proposed by the sponsor of evolocumab for the same indication (paragraph 7.15, evolocumab Public Summary Document (PSD), July 2019).

2 Background

Registration status

- 2.1 The current TGA-approved indication for alirocumab is as follows:

Primary hypercholesterolaemia

Alirocumab is indicated as an adjunct to diet and exercise to reduce LDL-c in adults with primary (heterozygous familial or non-familial) hypercholesterolaemia in patients with moderate to very high cardiovascular risk:

- In combination with a statin, or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with maximum tolerated dose of a statin,

- Alone or in combination with other lipid lowering therapies in patients who are statin intolerant or for whom a statin is contraindicated who are unable to reach LDL-C goals.

Prevention of cardiovascular events

Alirocumab is indicated to reduce the risk of cardiovascular events (myocardial infarction, stroke, unstable angina requiring hospitalisation) in adults with established cardiovascular disease, in combination with optimally dosed statins and/or other lipid-lowering therapies.

Previous PBAC consideration

- 2.2 At its March 2019 meeting, the PBAC considered a major submission for alirocumab for two indications. Alirocumab was recommended for the treatment of he-FH, but was not recommended for the treatment of non-FH in patients with previous acute coronary syndrome (ACS), diabetes mellitus and elevated LDL-c levels (≥ 2.6 mmol/L) based on an inadequately defined high-risk patient population, and a high and uncertain incremental cost-effectiveness ratio (ICER) (paragraph 7.1, alirocumab PSD, March 2019).
- 2.3 Following a deferral in July 2019, the PBAC recommended evolocumab at its November 2019 meeting for non-FH in patients with ASCVD who have an LDL level greater than 2.6 mmol/L and additional high-risk factors. The PBAC considered that the cost-effectiveness of evolocumab would be acceptable at the price proposed in the minor resubmission, and if use is confined to this high-risk population (PBAC outcomes, November 2019). Outcomes from the November 2019 PBAC meeting had not been published at the time this minor resubmission was prepared.
- 2.4 The outstanding matters of concern from the March 2019 meeting are summarised in the table below.

For more detail on PBAC's view, see section 6 PBAC outcome.

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Table 1: PBAC matters of concern in previous consideration (March 2019)

Matters of concern		How the resubmission addresses it
Restriction	(Paragraph 7.21) Refinement of the proposed non-FH population to include those at highest risk of a cardiovascular event with an established risk level of 25% over 3 years. The PBAC advised that the high-risk group may include patients who have experienced ≥ 2 events in ≥ 2 vascular territories over a short period of time; or have recent ACS and other high risk criteria such as diabetes mellitus; or who have other combinations of high risk criteria such as those identified in the current PBS listing for ezetimibe.	The minor resubmission provided a revised restriction based on the PBAC's July 2019 advice for evolocumab for the non-FH population.
Comparator	(Paragraph 7.17) The PBAC considered placebo, the nominated main comparator in patients with non-FH with previous ACS and concomitant diabetes, to be appropriate. The PBAC agreed with the ESC that, whilst the resubmission did not consider evolocumab as a potential near market comparator, the ITC of the CV outcomes trials (in patients with non-FH) was informative and indicated similar results for the composite CV outcomes across the ODYSSEY OUTCOMES and FOURIER trials.	In view of the anticipated recommendation for listing, the minor resubmission nominated evolocumab as the main comparator.
Economic analysis	(Paragraph 7.21) Adjustment of the economic model based on the concerns raised in paragraph 7.19 in order to determine how to adjust the price. The PBAC considered the ICER would need to be lower than proposed in the current submission given the inherent uncertainties associated with estimating the number of events, including deaths, beyond the trial follow-up.	Listing is requested on a cost-minimisation basis versus evolocumab, consistent with the clinical claim of non-inferior efficacy and safety.
Financial estimates	(Paragraph 7.20) The PBAC noted the difficulties in defining a high-risk non-FH population with greatest benefit as outlined by the DUSC and considered revised financial estimates for the non-FH population only, including a more targeted high risk eligible population and reduced price to achieve a lower ICER, would need to address these concerns.	Requested to join the RSA proposed by the sponsor of evolocumab for the same indication. The resubmission stated that, if recommended for listing for the same indication, alirocumab is expected to substitute for evolocumab, with nil net financial implications to the Commonwealth.

Source: Compiled by the Secretariat. Paragraph references refer to the March 2019 alirocumab PBAC Public Summary Document (PSD).

3 Requested listing

- 3.1 The proposed initial and continuing treatment restrictions for alirocumab for the treatment of non-FH in patients with ASCVD and additional high-risk factors are identical to those proposed for evolocumab from July 2019 (pages 2-3, evolocumab PSD, July 2019).
- 3.2 The minor resubmission did not request a grandfather restriction.
- 3.3 Suggestions and additions proposed by the PBAC to the requested listing are in italics and deletions are in strikethrough.

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Name, restriction, manner of administration, form	PBS item code	Max. Qty (packs)	Max. Qty (units)	No. of repeats	Published Dispensed price for max. qty	Proprietary name and manufacturer
ALIROCUMAB alirocumab 75 mg/mL injection, 2 x 1 mL injection devices	NEW	1	2	5	\$ [REDACTED]	Praluent® Sanofi-Aventis
alirocumab 150 mg/mL injection, 2 x 1 mL injection devices	NEW	1	2	5	\$ [REDACTED]	Praluent® Sanofi-Aventis

Initial treatment (non-familial hypercholesterolaemia)

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – Telephone/Emergency/Electronic
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.
Administrative Advice: Special Pricing Arrangements apply.
Administrative Advice: Authority applications for initial treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
Episodicity: [nil]
Severity: [nil]
Condition: Non-familial hypercholesterolaemia
PBS indication: Non-familial hypercholesterolaemia
Treatment Phase: Initial treatment
Clinical criteria:
The treatment must be in conjunction with dietary therapy and exercise
AND
Clinical criteria:
Patient must not be receiving concomitant PBS-subsidised treatment with another drug that belongs to the same class (a monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9)) as this drug
AND
Clinical criteria:
Patient must have symptomatic atherosclerotic cardiovascular disease
AND
Clinical criteria:
Patient must have an LDL cholesterol level in excess of 2.6 millimoles per litre prior to commencing treatment with a monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9)
AND
Clinical criteria:
Patient must have atherosclerotic disease in two or more vascular territories (as per the symptomatic atherosclerotic cardiovascular disease criteria) (coronary, cerebrovascular or peripheral vascular territories); or
Patient must have severe multi-vessel coronary heart disease defined as at least 50% stenosis in at least two large vessels; or
Patient must have had at least two major cardiovascular events (i.e. myocardial infarction, unstable angina, stroke or unplanned revascularisation) in the previous 5 years; or
Patient must have diabetes mellitus with microalbuminuria; or
Patient must have diabetes mellitus and be aged 60 years or more; or
Patient must be an Aboriginal or Torres Strait Islander with diabetes mellitus; or
Patient must have a Thrombolysis in Myocardial Infarction (TIMI) risk score for secondary prevention (TRS2°P); of four 4 or higher
Clinical criteria:
Statin tolerant

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<p>Patient must have been treated with the maximum recommended and or tolerated dose of atorvastatin (80 mg) or rosuvastatin (40 mg) according to the TGA-approved Product Information for at least a total of 12 consecutive weeks in conjunction with dietary therapy and exercise; or</p>
<p>Statin intolerant/contraindicated: Patient must have developed clinically important product-related adverse events necessitating withdrawal of statin treatment to trials of each of atorvastatin and rosuvastatin; or</p>
<p>Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information</p>
<p>AND</p>
<p>Clinical criteria: Patient must have been treated with ezetimibe for at least 12 consecutive weeks in conjunction with a statin (if tolerated), dietary therapy and exercise.</p>
<p>Treatment criteria: Must be treated by or in consultation with a specialist physician.</p>
<p>Prescribing Instructions: Symptomatic atherosclerotic cardiovascular disease is defined as: (i) The presence of symptomatic coronary artery disease (prior MI myocardial infarction or prior revascularisation procedure or angina associated with demonstrated significant coronary artery disease ($\geq 50\%$ or greater stenosis in ≥ 1 or more coronary arteries on imaging), or positive functional testing (e.g. myocardial perfusion scanning or stress echocardiography)); or (ii) The presence of symptomatic cerebrovascular disease (prior ischaemic stroke or revascularisation procedure, or transient ischaemic attack associated with $\geq 50\%$ or greater stenosis in ≥ 1 or more cerebral arteries on imaging); or (iii) The presence of symptomatic peripheral arterial disease (prior acute ischaemic event due to atherosclerosis or prior revascularisation procedure, or symptoms of ischaemia with evidence of significant peripheral artery disease ($\geq 50\%$ or greater stenosis in ≥ 1 or more peripheral arteries on imaging)).</p>
<p>Prescribing Instructions: The qualifying LDL cholesterol level must be provided at the time of application and must be no more than 2 months old. The qualifying LDL cholesterol level following at least 12 consecutive weeks of combined treatment with a statin, ezetimibe, dietary therapy and exercise (unless treatment with a statin is contraindicated, or following completion of statin trials as described in these prescriber instructions in the event of clinically important adverse events) must be stated at the time of application, documented in the patient's medical records and must be no more than 8 weeks old prior to commencing treatment with a monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9).</p>
<p>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.</p>
<p>Prescribing instructions: The date of the consultation with a specialist physician must be no more than 6 months prior to the application date. The full name of the specialist physician consulted and the date of consultation are to be provided at the time of application.</p>
<p>Prescribing instructions: The physician must attempt to treat the patient with the maximum recommended dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily).</p>
<p>Prescribing Instructions: If treatment with atorvastatin or rosuvastatin results in development of a clinically important product-related adverse event resulting in treatment withdrawal, the patient must be treated with the alternative statin (atorvastatin or rosuvastatin) unless there is a contraindication (e.g. prior rhabdomyolysis) to the alternative statin. This retreatal should occur after a washout period of at least 1 month, or if the creatine kinase (CK) level is elevated retreatal should not occur until CK has returned to normal.</p>
<p>Prescribing Instructions: In the event of a trial of an the alternative statin, it is recommended that the patient is started with the minimum dose of statin in conjunction with ezetimibe. The dose of the alternative statin should be increased not more often than every 4 weeks until the recommended or maximum tolerated dose has been reached or target LDL-c has been achieved.</p>
<p>Prescribing Instructions: At the time of application, one of the following must be provided: One of the following must be stated at the time of application and documented in the patient's medical records regarding prior statin treatment:</p>

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<p>(i) Confirmation that the patient was treated with atorvastatin 80 mg or rosuvastatin 40 mg or <i>the maximum tolerated dose of either for 12 consecutive weeks</i>; or</p> <p>(ii) The doses, and duration of treatment and details of adverse events experienced with trials with each of atorvastatin and rosuvastatin; or</p> <p>(iii) Confirmation That the patient is contraindicated to treatment with a statin as defined in the TGA-approved Product Information.</p> <p>(iv) The date of consultation and the full name of the specialist physician must be recorded in the patient's medical records; and</p> <p>(v) The result of LDL cholesterol level and one of the following where appropriate: statin treatment details including agent, dose and treatment duration; or details of adverse event or contraindication to treatment with a statin as defined in the TGA-approved Product Information must be recorded in the patient's medical records.</p> <p>Prescribing Instructions: <i>One or more of the following must be stated at the time of application and documented in the patient's medical records regarding the presence of cardiovascular disease or high risk of experiencing a cardiovascular event:</i></p> <p>(i) <i>Atherosclerotic disease in two or more vascular territories (coronary, cerebrovascular or peripheral vascular territories); or</i></p> <p>(ii) <i>Severe multi-vessel coronary heart disease defined as at least 50% stenosis in at least two large vessels; or</i></p> <p>(iii) <i>History of at least two major cardiovascular events (i.e. myocardial infarction, unstable angina, stroke or unplanned revascularisation) in the previous 5 years; or</i></p> <p>(iv) <i>Diabetes mellitus with microalbuminuria; or</i></p> <p>(v) <i>Diabetes mellitus and age 60 years or more; or</i></p> <p>(vi) <i>Aboriginal or Torres Strait Islander with diabetes mellitus; or</i></p> <p>(vii) <i>A Thrombolysis in Myocardial Infarction (TIMI) risk score for secondary prevention of 4 or higher</i></p> <p>Administrative Advice: <i>Authorisation under this restriction may also be made in real time using the Online PBS Authorities system (see www.humanservices.gov.au/HPOS).</i></p>

Continuing treatment (non-familial hypercholesterolaemia)

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Level / Method: <input checked="" type="checkbox"/> Streamlined [new code]
Administrative Advice: <i>No increase in the maximum quantity or number of units may be authorised.</i>
Administrative Advice: <i>No increase in the maximum number of repeats may be authorised.</i>
Administrative Advice: <i>Special Pricing Arrangements apply.</i>
Episodicity: [nil]
Severity: [nil]
Condition: <i>Non-familial hypercholesterolaemia</i>
PBS indication: <i>Non-familial hypercholesterolaemia</i>
Treatment Phase: 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 conjunction with dietary therapy and exercise

- 3.4 The minor resubmission stated that an effective price was not proposed for alirocumab as the effective price for evolocumab was unknown to the sponsor, and listing was requested on a cost-minimisation basis versus evolocumab.
- 3.5 The alirocumab Product Information recommended starting dose for all indications is 75 mg administered once every two weeks (Q2W) or 300 mg every four weeks (Q4W) based on patient preference. In March 2019, the PBAC recommended that a clinical criterion be included in the alirocumab restriction for he-FH: “Patient must commence initial treatment on a dose of 75 mg per fortnight or 300 mg per month”. The PBAC considered this may no longer be necessary as initial treatment is limited to specialist

physicians, rather than GPs, and there may be an implied understanding that specialists would prescribe in line with the Product Information but may require the flexibility to tailor the dose if deemed clinically appropriate. In terms of the maximum quantity, the Initial treatment listing facilitates either starting dose.

- 3.6 The PBAC considered that combination use of alirocumab and other proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors (i.e. evolocumab) should not be permitted, but that switching between the PCSK9 inhibitors should be permitted. The PBAC considered that these changes should also flow-on to the evolocumab listing for non-FH (which the PBAC recommended in November 2019, but not yet listed at the time of the March 2020 PBAC meeting), and the alirocumab listing for he-FH (which the PBAC recommended in March 2019, but not yet listed at the time of the March 2020 PBAC meeting).
- 3.7 Further, the PBAC considered that the following changes should flow-on to the recommended restriction for alirocumab in the he-FH setting:
- the Authority approval method should be amended from written to telephone/electronic in initial and grandfather treatment and from telephone/electronic to streamlined in continuing treatment for consistency with the recommended authority approval methods specified for evolocumab at the November 2019 PBAC meeting;
 - for consistency, the LDL-c eligibility threshold should be changed from 3.3 mmol/L to 2.6 mmol/L for patients with symptomatic ASCVD;
 - the clinical criterion “Patient must commence initial treatment on a dose of 75 mg per fortnight or 300 mg per month” should be removed, given that initial treatment excludes prescribing by non-specialist physicians; and
 - minor amendments to the administrative advice and prescriber instructions to align with the recommendation for evolocumab in November 2019.

For more detail on PBAC’s view, see section 6 PBAC outcome.

4 Comparator

- 4.1 The minor resubmission nominated evolocumab as the main comparator.
- 4.2 The previous major submission considered by the PBAC in March 2019 nominated placebo (standard of care) as the main comparator for the non-FH population, which the PBAC considered to be appropriate. An indirect treatment comparison (ITC) of alirocumab and evolocumab was also presented. In March 2019, the PBAC considered that, whilst the resubmission did not consider evolocumab as a potential near market comparator, the ITC of the CV outcomes trials (in patients with non-FH) was informative and indicated similar results for the composite CV outcomes across the ODYSSEY OUTCOMES and FOURIER trials (paragraph 7.17, alirocumab PSD, March 2019).

For more detail on PBAC’s view, see section 6 PBAC outcome.

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

5.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

5.3 The key clinical evidence presented in this minor resubmission was unchanged from that previously considered by the PBAC in March 2019. That is, an indirect comparison of cardiovascular outcomes with alirocumab (ODYSSEY OUTCOMES) versus evolocumab (FOURIER) in predominately non-FH populations with high cardiovascular risk.

5.4 The key features of the included trials are summarised in the table below.

Table 2: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes
Alirocumab trials					
ODYSSEY OUTCOMES	18,924	MC, R, DB, PC Median follow-up of 2.8 years	Low	Hypercholesterolaemia with recent ACS event	Cardiovascular events, lipid parameters
Evolocumab trials					
FOURIER	27,564	MC, R, DB, PC Approximately 2 year duration	Low	Hypercholesterolaemia with atherosclerotic disease	Cardiovascular events, lipid parameters

Source: Table 4, alirocumab PSD, March 2019

Abbreviations: ACS, acute coronary syndrome; DB, double blind; LDL, low density lipoprotein cholesterol; MC, multi-centre; PC, placebo-controlled; R, randomised

5.5 The PBAC previously considered there were exchangeability issues between the two trials in terms of the inclusion criteria of the trials, the definitions of cardiovascular endpoints (particularly components contributing to composite endpoints), baseline cardiovascular risk, circumstances of use of treatments, background lipid lowering therapies and follow-up duration. These differences are highlighted by the variability in the incidence of events occurring in the common reference arm for myocardial infarction, unstable angina and cardiovascular death.

Comparative effectiveness

Comparative efficacy in the ITT populations

5.6 The March 2019 alirocumab submission presented an ITC of the primary outcomes of ODYSSEY OUTCOMES and FOURIER in the intention-to-treat (ITT) populations. As shown in Table 3, there were differences in the components of these outcomes, i.e.

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ODYSSEY OUTCOMES included coronary heart disease death in its primary composite endpoint rather than cardiovascular death, while FOURIER included coronary revascularisation as an additional component.

Table 3: Primary outcomes of ODYSSEY OUTCOMES and FOURIER

ODYSSEY OUTCOMES	FOURIER
Primary efficacy outcome	Primary efficacy outcome
First occurrence of MACE including: <ul style="list-style-type: none">• coronary heart disease death,• non-fatal myocardial infarction,• fatal and non-fatal ischaemic stroke, or• unstable angina requiring hospitalisation	First occurrence of a MACE including: <ul style="list-style-type: none">• cardiovascular death,• myocardial infarction,• stroke,• hospitalisation for unstable angina or• coronary revascularisation

Source: Table 1.4, p7 of the minor resubmission

Abbreviation: MACE = Major adverse cardiovascular events

5.5 Due to these differences, additional analyses were presented where the components of the primary efficacy outcome were matched to FOURIER. A comparison of the secondary outcome of all-cause mortality was also presented. The results of ODYSSEY OUTCOMES, FOURIER and the resulting ITCs of alirocumab and evolocumab based on the ITT populations for the efficacy outcomes are summarised in Table 4 (this is unchanged from the previous submission).

Table 4: Indirect analyses comparing alirocumab with evolocumab based on cardiovascular outcomes

Trial	Alirocumab, n/N (%)	Placebo, n/N (%)	Evolocumab, n/N (%)	HR (95% CI)
Time to coronary death, non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, or unstable angina requiring hospitalisation (ODYSSEY OUTCOMES); or Time to cardiovascular death, myocardial infarction, stroke, unstable angina requiring hospitalisation, or coronary revascularisation (FOURIER)				
ODYSSEY OUTCOMES	903/9462 (9.5%)	1052/9462 (11.1%)	-	0.85 (0.78, 0.93)
FOURIER	-	1563/13780 (11.3%)	1344/13784 (9.8%)	0.85 (0.79, 0.92)
Alirocumab vs evolocumab				1.00 (0.89, 1.13)
Time to fatal or non-fatal myocardial infarction				
ODYSSEY OUTCOMES	646/9462 (6.8%)	756/9462 (8.0%)	-	0.85 (0.76, 0.94)
FOURIER	-	639/13780 (4.6%)	468/13784 (3.4%)	0.73 (0.65, 0.82)
Alirocumab vs evolocumab				1.16 (0.99, 1.36)
Time to fatal or non-fatal ischaemic stroke (ODYSSEY OUTCOMES); or Time to stroke including ischaemic, haemorrhagic or unknown (FOURIER)				
ODYSSEY OUTCOMES	111/9462 (1.2%)	152/9462 (1.6%)	-	0.73 (0.57, 0.93)
FOURIER	-	262/13780 (1.9%)	207/13784 (1.5%)	0.79 (0.66, 0.95)
Alirocumab vs evolocumab				0.97 (0.71, 1.33)
Time to unstable angina requiring hospitalisation				
ODYSSEY OUTCOMES	37/9462 (0.4%)	60/9462 (0.6%)	-	0.61 (0.41, 0.92)
FOURIER	-	239/13780 (1.7%)	236/13784 (1.7%)	0.99 (0.82, 1.18)
Alirocumab vs evolocumab				0.62 (0.40, 0.96)
Time to ischaemia-driven coronary revascularisation (ODYSSEY OUTCOMES); or Time to coronary revascularisation (FOURIER)				
ODYSSEY OUTCOMES	731/9462 (7.7%)	828/9462 (8.8%)	-	0.88 (0.79, 0.97)
FOURIER	-	965/13780 (7.0%)	759/13784 (5.5%)	0.78 (0.71, 0.86)
Alirocumab vs evolocumab				1.13 (0.98, 1.30)
Time to cardiovascular death				
ODYSSEY OUTCOMES	240/9462 (2.5%)	271/9462 (2.9%)	-	0.88 (0.74, 1.05)
FOURIER	-	240/13780 (1.7%)	251/13784 (1.8%)	1.05 (0.88, 1.25)
Alirocumab vs evolocumab				0.84 (0.65, 1.07)
Time to death from any cause				
ODYSSEY OUTCOMES	334/9462 (3.5%)	392/9462 (4.1%)	-	0.85 (0.73, 0.98)
FOURIER	-	426/13780 (3.1%)	444/13784 (3.2%)	1.04 (0.91, 1.19)
Alirocumab vs evolocumab				0.82 (0.67, 1.00)

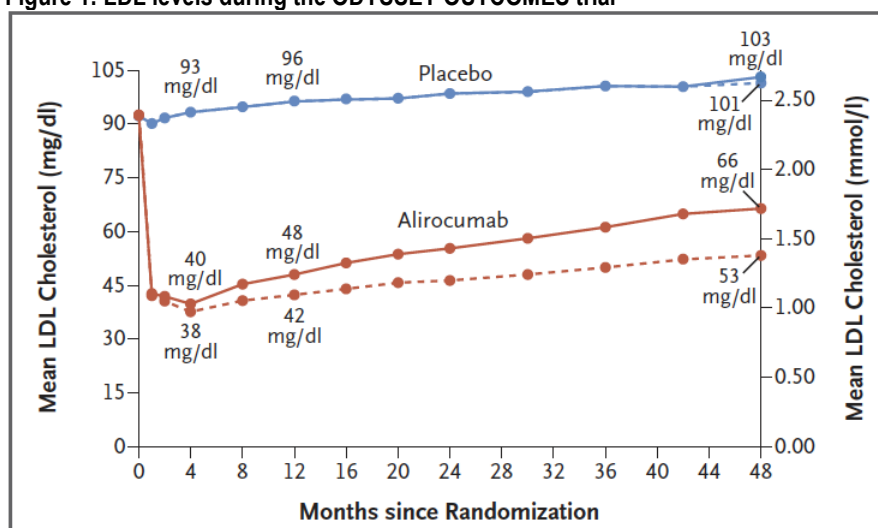
Source: Table 1.5, p8 of the minor resubmission; March 2019 alirocumab PSD, Table 7, p19

- 5.6 The PBAC noted there were no statistically significant differences in cardiovascular events when comparing alirocumab with evolocumab using placebo as a common reference, except for unstable angina requiring hospitalisation with results in favour of alirocumab (paragraph 6.25, alirocumab PSD, March 2019). The PBAC previously considered the indirect comparison to be informative, but noted there were exchangeability issues between the trials.
- 5.7 In its previous consideration of alirocumab for the **he-FH population** (and in the context of supportive indirect analyses being available from other lipid outcomes trials

in the he-FH population), the PBAC considered: “There is no established non-inferiority margin for the major adverse cardiovascular events (MACE) outcomes used in the ITC but the PBAC considered the hazard ratio (HR) of 1.00 (95% CI, 0.89-1.13) for the primary composite endpoint supported similar outcomes across the trials given the upper CI was within the estimated difference for both treatments compared to placebo (approximately 15% for both interventions). Non-inferiority based on the CV outcomes for he-FH was not definitive given the limitations with the indirect analyses of the ODYSSEY OUTCOMES and FOURIER trials” (paragraph 7.6, alirocumab PSD, March 2019).

- 5.8 The pre-PBAC response acknowledged the exchangeability issues, but argued that the ITC represents the best available evidence to inform a clinical claim of comparative efficacy using patient-relevant CV outcomes and safety versus evolocumab in patients with non-FH.
- 5.9 In its previous consideration, the PBAC expressed concerns regarding the attenuation of LDL reduction and convergence in cardiovascular event rates over time that were observed in the ODYSSEY OUTCOMES trial. Figure 1 presents LDL levels during the ODYSSEY OUTCOMES trial from the ITT analysis (shown in solid lines) and on-treatment analysis (shown in dashed lines).

Figure 1: LDL levels during the ODYSSEY OUTCOMES trial



Source: Figure 1, p6 of the Schwartz (2018) publication

Note 1: To convert the LDL values to millimoles per litre, multiply by 0.02586

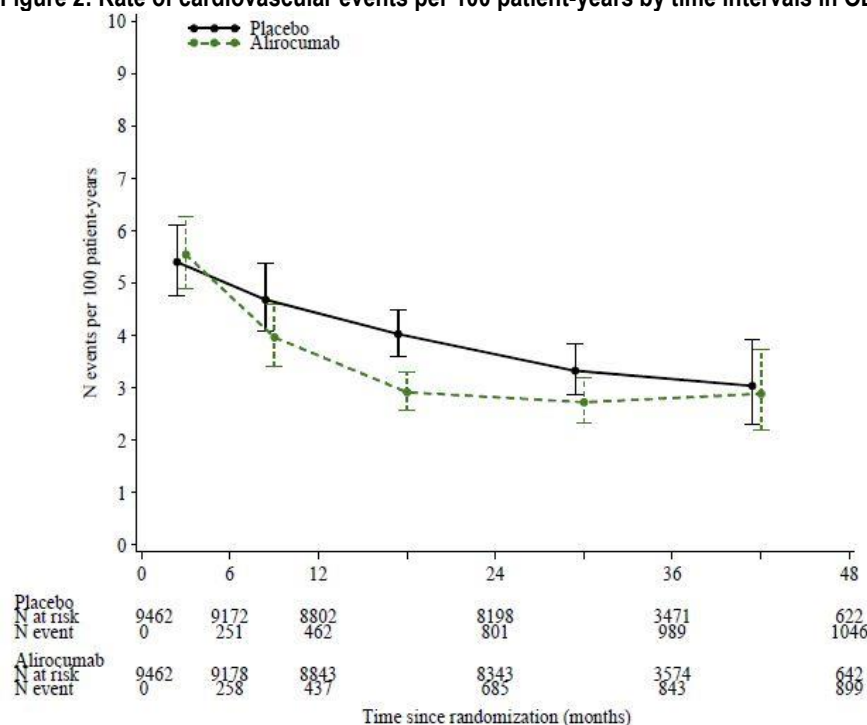
Note 2: ITT analysis (shown in solid lines) and on-treatment analysis (shown in dashed lines)

- 5.10 Treatment with alirocumab 75/150 mg was associated with a mean LDL reduction of 39.9% versus placebo at Month 48 (95% CI -44.6, -35.2). The greatest mean reduction in LDL associated with alirocumab compared with placebo was 60.1% observed at Month 4, which attenuated over time to 53.7% at Month 12 to 39.9% at Month 48. The previous submission claimed that the attenuation in LDL-c reduction may be due to the dosing algorithm that allowed for down-titrations and/or switching to placebo and the use of LDL targets (between 0.78 to 1.29 mmol/L) which was different to

previous trials of alirocumab with lipid outcomes. The PBAC considered that it was unclear whether the attenuation of effect over time was due to a loss of efficacy or down-titration.

5.11 Figure 2 presents an analysis of time to first occurrence of MACE by time intervals for the ITT population.

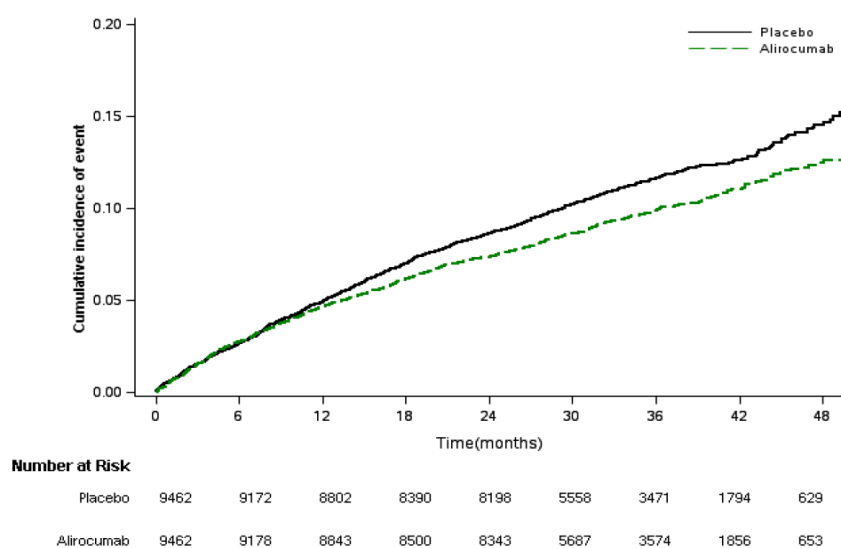
Figure 2: Rate of cardiovascular events per 100 patient-years by time intervals in ODYSSEY OUTCOMES



Source: Figure 16.2.6.1.2.2 (section 16.2.6) of the clinical trial report

5.12 The curves indicate divergence by 6 months with peak difference at approximately 18 months and convergence towards the end of the trial. The pre-PBAC response argued that this analysis biases against alirocumab particularly at later time points where there are fewer patients left at risk especially in the placebo treatment group (as the analysis was based on the numbers of patients who had not experienced an event in the previous time interval and who were not censored in a previous time interval). The pre-PBAC response further argued that the rate of events based on cumulative incidence (shown in Figure 3) was more informative as it was not impacted by this potential bias. The pre-PBAC response stated that the cumulative incidence of MACE in ODYSSEY OUTCOMES showed increasing divergence between alirocumab versus placebo for the primary outcome.

Figure 3: Cumulative incidence of MACE in ODYSSEY OUTCOMES



Source: Figure 1 of the pre-PBAC response.

- 5.13 The previous pre-PBAC response also provided analyses of time to first occurrence of MACE using the subgroup of patients with LDL-C ≥ 2.6 mmol/L, which showed a continued divergence of the curves. However, the PBAC previously considered that the pattern of convergence in the ITT population remained inadequately explained. There was no similar convergence observed in the FOURIER trial. Overall, the PBAC previously considered the alirocumab findings were not adequately explained by the dosing algorithm that allowed for down-titrations and/or switching to placebo and the use of LDL targets (between 0.78 to 1.29 mmol/L) in the ODYSSEY OUTCOMES trial (paragraph 7.18, alirocumab PSD, March 2019).
- 5.14 The PBAC recalled, from its previous consideration, that the results from the ODYSSEY OUTCOMES trial report suggest a 25% reduction in cardiovascular risk per 1 mmol/L decrease in LDL with alirocumab treatment (HR 0.75, 95% CI 0.72, 0.78). The trial report noted that this was consistent with Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis that suggested a 22% risk reduction per 1 mmol/L decrease in LDL. The results were also broadly consistent with landmark analyses from the FOURIER trial suggesting relative risk reductions in major coronary events per 1 mmol/L reduction in LDL (Year 1: HR 0.87, 95% CI 0.79, 0.97; Year 2: HR 0.80, 95% CI 0.71, 0.90; reported in Sabatine 2017) (paragraph 6.17, alirocumab PSD, March 2019).

Supportive analyses of efficacy (new data, not presented in the previous submission)

- 5.15 As the July 2019 public summary document for evolocumab presented results for several subgroups of patients from FOURIER who were considered to have a high risk of a future CV event, the current submission also presented additional ITCs with corresponding data from ODYSSEY OUTCOMES. The data from FOURIER that were presented in the public summary document were for the key secondary outcome,

while corresponding data from ODYSSEY OUTCOMES were only available for the primary efficacy outcomes (see Table 5).

Table 5: Primary outcome of ODYSSEY OUTCOMES and key secondary outcome of FOURIER

ODYSSEY OUTCOMES	FOURIER
Primary efficacy outcome	Key secondary efficacy outcome
First occurrence of MACE including: <ul style="list-style-type: none"> coronary heart disease death, non-fatal myocardial infarction, fatal and non-fatal ischaemic stroke, or unstable angina requiring hospitalisation 	First occurrence of a MACE including: <ul style="list-style-type: none"> cardiovascular death, myocardial infarction, stroke

Source: Table 1.6, p9 of the minor resubmission

Abbreviation: MACE = Major adverse cardiovascular events

5.16 The results of the ITCs of alirocumab versus evolocumab in the identified high-risk subgroups and the complements of the subgroups are presented in Table 6. The resubmission noted the following differences between the data available: ODYSSEY OUTCOMES used a 9-point TIMI score, while FOURIER used a modified 10-point scale; and ODYSSEY OUTCOMES did not collect data on multivessel disease. The data presented in Table 6 includes patients irrespective of LDL-C levels (while the restriction specifies use in patients with LDL-C > 2.6 mmol/L) to align with the FOURIER data presented in the evolocumab PSD.

5.17 As this was a minor submission, the additional analyses were not verified.

Table 6: Indirect treatment comparison alirocumab versus evolocumab (high-risk subgroups): first occurrence of MACE

Population	Trial	Alirocumab, n/N (%)	Placebo, n/N (%)	Evolocumab, n/N (%)	HR (95% CI)
ITT	ODYSSEY OUTCOMES	903/9,462 (9.5%)	1052/9,462 (11.1%)	-	0.85 (0.78, 0.93)
	FOURIER	-	1,013/13,780 (9.9%)~	816/13,784 (7.9%)~	0.80 (0.73, 0.88)
	Alirocumab vs evolocumab				1.06 (0.93, 1.21)
Diabetes subgroup	ODYSSEY OUTCOMES	380/2693 (14.5%)	452/2751 (16.4%)	-	0.84 (0.74, 0.97)
	FOURIER	-	508/5516 (12.2%)~	417/5515 (10.2%)~	0.82 (0.72, 0.93)
	Alirocumab vs evolocumab				1.02 (0.85, 1.23)
No diabetes subgroup	ODYSSEY OUTCOMES	523/6769 (7.7%)	600/6,711 (8.9%)	-	0.86 (0.76, 0.96)
	FOURIER	-	505/8,264 (8.4%)~	399/8,269 (6.4%)~	0.78 (0.69, 0.89)
	Alirocumab vs evolocumab				1.10 (0.93, 1.31)
Polyvascular disease subgroup	ODYSSEY OUTCOMES	163/779 (20.9%)	186/775 (24.0%)	-	0.86 (0.69, 1.06)
	FOURIER	-	NR/NR (16.7%)~	NR/NR (16.0%)~	0.86 (0.71, 1.04)
	Alirocumab vs evolocumab				1.00 (0.75, 1.33)
No polyvascular disease subgroup	ODYSSEY OUTCOMES	740/8,683 (8.5%)	866/8,687 (10.0%)	-	0.85 (0.77, 0.93)
	FOURIER	-	NR	NR	NR
	Alirocumab vs evolocumab				-

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Population	Trial	Alirocumab, n/N (%)	Placebo, n/N (%)	Evolocumab, n/N (%)	HR (95% CI)
Low risk TIMI	ODYSSEY OUTCOMES [^]	249/4,510 (5.5%)	298/4,546 (6.6%)	-	0.84 (0.71, 0.99)
	FOURIER [*]	-	NR (5.0%)~	NR (3.8%)~	0.73 (0.43, 1.23)
	Alirocumab vs evolocumab				1.15 (0.66, 2.00)
Intermediate risk TIMI	ODYSSEY OUTCOMES [^]	256/2,816 (9.1%)	308/2,754 (11.2%)	-	0.80 (0.68, 0.94)
	FOURIER [*]	-	NR (8.6%)~	NR (6.7%)~	0.79 (0.71, 0.89)
	Alirocumab vs evolocumab				1.01 (0.83, 1.23)
High risk TIMI	ODYSSEY OUTCOMES [^]	398/2,136 (18.6%)	446/2,162 (20.6%)	-	0.89 (0.78, 1.02)
	FOURIER [*]	-	NR (19.1%)~	NR (15.5%)~	0.80 (0.67, 0.95)
	Alirocumab vs evolocumab				1.11 (0.89, 1.39)
Prior stroke vs MI subgroup with multiple events	ODYSSEY OUTCOMES	61/306 (19.9%)	77/305 (25.2%)	-	0.77 (0.55, 1.07)
	FOURIER	-	320/2,628 (15.0%)~	NR/2,657 (12.4%)~	0.79 (0.67, 0.94)
	Alirocumab vs evolocumab				0.97 (0.67, 1.42)
No prior stroke vs MI subgroup without multiple events	ODYSSEY OUTCOMES	842/9,156 (9.2%)	975/9,157 (10.6%)	-	0.85 (0.78, 0.94)
	FOURIER	-	512/8,570 (8.2%)~	NR/8,477 (6.6%)~	0.84 (0.74, 0.96)
	Alirocumab vs evolocumab				1.01 (0.86, 1.19)
Prior CABG vs MI subgroup with multivessel disease	ODYSSEY OUTCOMES	123/502 (24.5%)	155/501 (30.9%)	-	0.77 (0.61, 0.98)
	FOURIER	-	272/2,806 (12.6%)~	NR/2,812 (9.2%)~	0.70 (0.58, 0.84)
	Alirocumab vs evolocumab				1.10 (0.81, 1.49)
Index CABG vs MI subgroup without multivessel disease	ODYSSEY OUTCOMES	33/494 (6.7%)	40/531 (7.5%)	-	0.85 (0.54, 1.35)
	FOURIER	-	556/8,390 (8.9%)~	NR/8,325 (7.6%)~	0.89 (0.79, 1.00)
	Alirocumab vs evolocumab				0.96 (0.60, 1.53)
No prior CABG vs MI subgroup without multivessel disease	ODYSSEY OUTCOMES	747/8,466 (8.8)	857/8,430 (10.2%)	-	0.86 (0.78, 0.95)
	FOURIER	-	556/8,390 (8.9%)~	NR/8,325 (7.6%)~	0.89 (0.79, 1.00)
	Alirocumab vs evolocumab				0.97 (0.83, 1.13)

Source: Table 1.7, p10 of the minor resubmission; ODYSSEY OUTCOMES CSR report body, p155, p157; Jukema et al. (2019), Supplementary Online Table 1, p3; Goodman et al. (2019), Table 3, p1184; July 2019 evolocumab PSD, Table 7, pp26-28

Abbreviations: CABG = coronary artery bypass graft; MI = myocardial infarction; NR = not reported; TIMI = Thrombolysis in Myocardial Infarction

~ The evolocumab PSD July 2019 reports the event incidence (n), total patients (N) and the three-year Kaplan-Meier estimates (%)

[^] ODYSSEY OUTCOMES, low-risk was defined as 0 points, intermediate risk was defined as 1 to 2 points, and high risk as ≥ 3 points on a 9-point scale (Bohula et al., 2016)

^{*} In FOURIER, low-risk was defined as 1-point, intermediate TIMI risk was defined as 2-4 points and high TIMI risk was defined as ≥ 5 points on the modified 10-point scale

Dose titration

- 5.18 In ODYSSEY OUTCOMES, patients in the alirocumab arm were commenced on a dose of 75 mg fortnightly for two months, after which time patients were treated to target and could receive a dose of either 75 mg or 150 mg fortnightly adjusted to achieve LDL-c levels between 0.78 to 1.29 mmol/L. On the other hand, FOURIER was a fixed dose trial, that is, patients were treated with evolocumab at either dose (140 mg fortnightly or 420 mg monthly) according to their preference.
- 5.19 The minor resubmission presented a summary of the proportion of patients whose dose was titrated in the alirocumab arm of ODYSSEY OUTCOMES (see Table 7).

Table 7: Titration in the alirocumab arm of ODYSSEY OUTCOMES

	Alirocumab, n (%)
Patients initiated on 75 mg Q2W	9,451 (100%)
Up-titration to 150 mg Q2W*	2,615 (27.7%)
Subsequently down-titration to 75 mg Q2W	805 (8.5%)
Switch to placebo afterwards ^a	5 (<0.1%)
Switch to placebo injection ^a	730 (7.7%)

Source: Table 1.9, p13 of the minor resubmission; ODYSSEY OUTCOMES CSR, p43, Table 34, p179

Abbreviation: Q2W = fortnightly

^a Due to two consecutive LDL-C < 15 mg/dL (< 0.39 mmol/L)

*Time of up-titration: 2,536 patients at Month 2 (2536/2615; 26.8%) and 79 patients at Month 4 (79/2615; 0.8%)

- 5.20 The minor resubmission stated that the titration of alirocumab allows doses to be individualised to each patient with the aim to treat with the lowest dose necessary to achieve the LDL-c target range, and that the treat to target approach results in a clinically significant reduction in CV events. Thus, the sponsor claimed that, while some patients require up-titration to 150 mg fortnightly to achieve the target LDL-c range, all patients experience the same efficacy in terms of CV risk reduction.
- 5.21 The minor resubmission therefore claimed that alirocumab 75 mg fortnightly and 150 mg fortnightly after dose titration is non-inferior to evolocumab 140 mg fortnightly or 420 mg monthly in terms of efficacy and safety.
- 5.22 In its previous consideration of alirocumab in the **he-FH population** (and based on data from trials that did not include ODYSSEY OUTCOMES), the PBAC “noted there was an approximately 20% difference in LDL reduction observed in subgroup analyses of patients receiving alirocumab who were up-titrated compared to those with no titration, and that the 75 mg fortnightly dose during initial treatment phases, up to 24 weeks, may result in reduced effectiveness when compared to the higher strengths of alirocumab. The PBAC was also concerned about the robustness of the non-inferiority claim given the wide confidence intervals and point estimates favouring evolocumab. The PBAC considered alirocumab was less efficacious at the lower strength (75 mg fortnightly) but the uncertainty in the ITC did not preclude the option of cost-minimisation with evolocumab for the higher alirocumab strength (150 mg fortnightly). The PBAC concluded that non-inferiority could only be supported for the up titrated dose of 150 mg fortnightly rather than on the analyses with the pooled doses of alirocumab” (paragraph 7.8, alirocumab PSD, March 2019).

5.23 The minor resubmission did not present efficacy results from ODYSSEY OUTCOMES by dosage regimen used. The pre-PBAC response stated that due to differences between patients treated with alirocumab 75mg Q2W and those up titrated to 150mg Q2W in terms of baseline LDL-c, a comparison between these groups is not possible.

Comparative harms

5.24 At its March 2019 meeting, the PBAC noted that no significant safety issues were identified, with injection site reactions being minor, and therefore considered that non-inferior safety of alirocumab versus evolocumab was reasonable (paragraph 7.10, alirocumab PSD, March 2019).

Clinical claim

5.25 The minor resubmission claimed non-inferior comparative effectiveness and non-inferior comparative safety compared with evolocumab.

5.26 The PBAC considered that the claim of non-inferior comparative effectiveness versus evolocumab was reasonable for the 150 mg fortnightly dose of alirocumab but was not adequately supported by the data for the 75 mg fortnightly (or 300 mg monthly) dose.

5.27 The PBAC considered that the claim of non-inferior comparative safety versus evolocumab was reasonable.

Economic analysis

5.28 The minor resubmission presented a cost-minimisation analysis for the comparison of alirocumab versus evolocumab for the requested non-FH population. The key assumptions and components of the analysis are summarised in Table 8.

Table 8: Key assumptions and components of the cost minimisation analysis

Component	Claim or assumption
Therapeutic efficacy claim	Based on evidence presented, the efficacy of alirocumab is non-inferior to evolocumab
Therapeutic safety claim	Based on evidence presented, the safety of alirocumab is non-inferior to evolocumab
Evidence base	ITC of randomised trials (ODYSSEY OUTCOMES and FOURIER)
Equi-effective doses	Alirocumab 75 mg Q2W and 150 mg Q2W are equi-effective to evolocumab 140 mg Q2W or 420 mg Q4W
Direct medicine costs	The effective price of evolocumab is unknown
Other costs or cost offsets	No

Abbreviations: Q2W = fortnightly; Q4W = four-weekly

5.29 The minor resubmission stated that, as an effective and published price for evolocumab for non-FH patients with ASCVD and additional high-risk factors has not yet been established, a formal cost-minimisation analysis cannot be conducted.

5.30 Whilst an effective price for alirocumab was not proposed, the sponsor requested a published approved ex-manufacturer price (AEMP) for alirocumab of \$ [REDACTED] and a corresponding published dispensed price for maximum quantity (DMPQ) of \$ [REDACTED].

- 5.31 The minor resubmission requested flat pricing across both the 75 mg and 150 mg strengths. The minor resubmission stated that alirocumab 75 mg every two weeks and alirocumab 150 mg every two weeks are equally effective in terms of a reduction in CV events after patients have titrated to a target LDL-C range. As noted above, in its March 2019 consideration of alirocumab for he-FH, the PBAC considered alirocumab was less efficacious at the lower strength (75 mg fortnightly) (paragraph 7.8, alirocumab PSD, March 2019).
- 5.32 In its recommendation of alirocumab for he-FH in March 2019, the PBAC advised that alirocumab 150 mg fortnightly is equi-effective to evolocumab 140 mg fortnightly or 420 mg monthly. The PBAC, whilst noting the sponsor's request for flat pricing, advised that a tiered pricing structure reflecting the recommended equi-effective doses would be appropriate in light of the uncertainty with the lower doses of alirocumab (75 mg fortnightly or 300 mg monthly) (paragraph 7.9, alirocumab PSD, March 2019).

Estimated PBS usage & financial implications

- 5.33 The minor resubmission stated that it anticipated that there would be a RSA in place for evolocumab with fixed expenditure caps. The minor resubmission further stated that if alirocumab is recommended for listing on the PBS for the same indication, "it is expected to substitute for evolocumab and will be required to join the RSA for the same indication".

For more detail on PBAC's view, see section 6 PBAC outcome.

6 PBAC Outcome

- 6.1 The PBAC recommended the Authority Required listing of alirocumab for the treatment of non-familial hypercholesterolaemia (non-FH) in patients with atherosclerotic cardiovascular disease (ASCVD), who have an LDL level greater than 2.6 mmol/L and additional high risk factors. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of alirocumab would be acceptable if it were cost-minimised against evolocumab. The PBAC advised that alirocumab should join the RSA subsidisation caps for evolocumab for the same indication and that there should be no net cost to Government.
- 6.2 The PBAC considered that the restriction, which was revised based on the PBAC's previous advice for evolocumab, adequately addressed the Committee's previous concerns by defining the high-risk subgroups who would derive the most benefit from treatment with alirocumab. The PBAC considered that the restriction for alirocumab should align with the restriction recommended for evolocumab in the non-FH setting.
- 6.3 The PBAC also recommended the following changes to the restriction requested in the minor resubmission:
- Additional wording in the clinical criteria and prescriber instructions to allow switching between alirocumab and other PCSK9 inhibitors (i.e. evolocumab).

- A new clinical criterion to prevent concomitant use of alirocumab with other PCSK9 inhibitors (i.e. evolocumab).
- 6.4 The PBAC considered evolocumab, the nominated main comparator, to be appropriate.
- 6.5 The key evidence presented was an ITC of cardiovascular outcomes with alirocumab (ODYSSEY OUTCOMES) versus evolocumab (FOURIER) in predominately non-FH patients with high cardiovascular risk. The PBAC considered the hazard ratio (HR) of 1.00 (95% CI, 0.89-1.13) for the primary composite endpoint supported similar outcomes across the trials, but re-iterated its previous consideration that the results were difficult to interpret due to exchangeability issues between the trials (including differences in the patient populations and some outcome measures). Further, the PBAC re-iterated its previous concerns regarding the convergence in cardiovascular event rates and attenuation of LDL-c reduction over time that were observed in the ODYSSEY OUTCOMES trial.
- 6.6 The PBAC recalled its previous concerns that alirocumab may be less efficacious at the lower (75 mg fortnightly) strength. These concerns were based on indirect analyses of lipid outcomes trials in the he-FH population that were presented in the previous submission. In its previous consideration, the PBAC noted there was an approximately 20% difference in LDL reduction observed in subgroup analyses of patients receiving alirocumab who were up-titrated compared to those with no titration, and that the 75 mg fortnightly dose during initial treatment phases (up to 24 weeks) may result in reduced effectiveness when compared to the higher strengths of alirocumab. The PBAC noted that the minor resubmission did not present efficacy results from ODYSSEY OUTCOMES by dosage regimen used.
- 6.7 The pre-PBAC response claimed that LDL-c reduction was a surrogate outcome and that the clinical evidence from ODYSSEY OUTCOMES (which was compared with the FOURIER trial in the ITC) was the most relevant for the non-FH population. However, the PBAC considered that the ITC was difficult to interpret given the concerns regarding the heterogeneity between trials in the ITC and the potential attenuation of effect of alirocumab.
- 6.8 On balance, the PBAC reiterated its previous consideration that alirocumab was less efficacious at the lower strength (75 mg fortnightly) but the uncertainty in the ITC did not preclude the option of cost-minimisation with evolocumab for the higher alirocumab strength (150 mg fortnightly). Consistent with the March 2019 consideration in the he-FH population, the PBAC concluded that non-inferiority could only be supported for the up-titrated dose of 150 mg fortnightly, and that non-inferiority had not been adequately established between alirocumab 75 mg fortnightly or alirocumab 300 mg monthly) and evolocumab 140 mg fortnightly (or 420 mg monthly).
- 6.9 The PBAC advised that alirocumab 150 mg fortnightly is equi-effective to evolocumab 140 mg fortnightly or 420 mg monthly. The PBAC, whilst noting the sponsor's request

for flat pricing, advised that a tiered pricing structure reflecting the recommended equi-effective doses would be appropriate in light of the uncertainty with the lower doses of alirocumab (75 mg fortnightly or 300 mg monthly).

- 6.10 To avoid the risk of less effective therapy being priced the same as evolocumab, the PBAC re-iterated its previous advice that pricing of the lower dose of alirocumab will be determined by the Department according to usual methods.
- 6.11 The PBAC considered that non-inferior safety of alirocumab versus evolocumab was reasonable.
- 6.12 The PBAC considered there should be no financial implications to the Commonwealth associated with the listing of alirocumab, as alirocumab would substitute for evolocumab in the same non-FH population. The PBAC advised that alirocumab should join the RSA for evolocumab for the same indication with no changes to the cap.
- 6.13 The PBAC considered that the changes outlined in paragraph 3.7 should also flow-on to alirocumab for he-FH.
- 6.14 The PBAC advised that, like evolocumab, alirocumab is not suitable for prescribing by nurse practitioners.
- 6.15 The PBAC advised that alirocumab should not be exempt from the Early Supply Rule.
- 6.16 The PBAC advised that, under section 101(3BA) of the National Health Act, alirocumab should be treated as interchangeable on an individual patient basis with evolocumab at the recommended equi-effective doses of alirocumab 150 mg fortnightly being equi-effective to evolocumab 140 mg fortnightly or 420 mg monthly.
- 6.17 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because alirocumab is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over evolocumab, or address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 6.18 The PBAC advised that this submission would not meet the criteria for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

7 Recommended listing

- 7.1 Add new items:

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Name, restriction, manner of administration, form	PBS item code	Max. Qty (packs)	Max. Qty (units)	No. of repeats	Proprietary name and manufacturer
ALIROCUMAB alirocumab 75 mg/mL injection, 2 x 1 mL injection devices	NEW	1	2	5	Praluent® Sanofi-Aventis
alirocumab 150 mg/mL injection, 2 x 1 mL injection devices	NEW	1	2	5	Praluent® Sanofi-Aventis

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – Telephone/Emergency/Electronic
Administrative Advice: No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.
PBS indication: Non-familial hypercholesterolaemia Treatment Phase: Initial treatment Clinical criteria: <ul style="list-style-type: none"> ▪ The treatment must be in conjunction with dietary therapy and exercise AND ▪ Patient must not be receiving concomitant PBS-subsidised treatment with another drug that belongs to the same class (a monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9)) as this drug AND ▪ Patient must have symptomatic atherosclerotic cardiovascular disease AND ▪ Patient must have an LDL cholesterol level in excess of 2.6 millimoles per litre prior to commencing treatment with a monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9) AND ▪ Patient must have atherosclerotic disease in two or more vascular territories (coronary, cerebral or peripheral territories); or ▪ Patient must have severe multi-vessel coronary heart disease defined as at least 50% stenosis in at least two large vessels; or ▪ Patient must have had at least two major cardiovascular events (i.e. myocardial infarction, unstable angina, stroke or unplanned revascularisation) in the previous 5 years; or ▪ Patient must have diabetes mellitus with microalbuminuria; or ▪ Patient must have diabetes mellitus and be aged 60 years or more; or ▪ Patient must be an Aboriginal or Torres Strait Islander with diabetes mellitus; or ▪ Patient must have a Thrombolysis in Myocardial Infarction (TIMI) risk score for secondary prevention of 4 or higher AND ▪ Patient must have been treated with the maximum recommended dose of atorvastatin (80 mg) or rosuvastatin (40 mg) according to the TGA-approved Product Information or the maximum tolerated dose of atorvastatin or rosuvastatin for at least 12 consecutive weeks in conjunction with dietary therapy and exercise; or ▪ Patient must have developed clinically important product-related adverse events necessitating withdrawal of statin treatment to trials of each of atorvastatin and rosuvastatin; or ▪ Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information AND ▪ Patient must have been treated with ezetimibe for at least 12 consecutive weeks in conjunction with a statin (if tolerated), dietary therapy and exercise. Treatment criteria: <ul style="list-style-type: none"> ▪ Must be treated by a specialist physician.

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Prescribing Instructions:

Symptomatic atherosclerotic cardiovascular disease is defined as:

- (i) The presence of symptomatic coronary artery disease (prior myocardial infarction, prior revascularisation procedure, angina associated with demonstrated significant coronary artery disease (50% or greater stenosis in 1 or more coronary arteries on imaging), or positive functional testing (e.g. myocardial perfusion scanning or stress echocardiography)); or
- (ii) The presence of symptomatic cerebrovascular disease (prior ischaemic stroke, prior revascularisation procedure, or transient ischaemic attack associated with 50% or greater stenosis in 1 or more cerebral arteries on imaging); or
- (iii) The presence of symptomatic peripheral arterial disease (prior acute ischaemic event due to atherosclerosis, prior revascularisation procedure, or symptoms of ischaemia with evidence of significant peripheral artery disease (50% or greater stenosis in 1 or more peripheral arteries on imaging)).

The qualifying LDL cholesterol level following at least 12 consecutive weeks of combined treatment with a statin, ezetimibe, dietary therapy and exercise (unless treatment with a statin is contraindicated, or following completion of statin trials as described in these prescriber instructions in the event of clinically important adverse events) must be stated at the time of application, documented in the patient's medical records and must be no more than 8 weeks old prior to commencing treatment with a monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9).

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.

If treatment with atorvastatin or rosuvastatin results in development of a clinically important product-related adverse event resulting in treatment withdrawal, the patient must be treated with the alternative statin (atorvastatin or rosuvastatin) unless there is a contraindication (e.g. prior rhabdomyolysis) to the alternative statin. This retreat should occur after a washout period of at least 4 weeks, or if the creatine kinase (CK) level is elevated retreat should not occur until CK has returned to normal.

In the event of a trial of the alternative statin, it is recommended that the patient is started with the minimum dose of statin in conjunction with ezetimibe. The dose of the alternative statin should be increased not more often than every 4 weeks until the recommended or maximum tolerated dose has been reached or target LDL-c has been achieved.

One of the following must be stated at the time of application and documented in the patient's medical records regarding prior statin treatment:

- (i) The patient was treated with atorvastatin 80 mg or rosuvastatin 40 mg or the maximum tolerated dose of either for 12 consecutive weeks; or
- (ii) The doses, duration of treatment and details of adverse events experienced with trials with each of atorvastatin and rosuvastatin; or
- (iii) The patient is contraindicated to treatment with a statin as defined in the TGA-approved Product Information.

One or more of the following must be stated at the time of application and documented in the patient's medical records regarding the presence of cardiovascular disease or high risk of experiencing a cardiovascular event:

- (i) Atherosclerotic disease in two or more vascular territories (coronary, cerebral or peripheral territories); or
- (ii) Severe multi-vessel coronary heart disease defined as at least 50% stenosis in at least two large vessels; or
- (iii) History of at least two major cardiovascular events (i.e. myocardial infarction, unstable angina, stroke or unplanned revascularisation) in the previous 5 years; or
- (iv) Diabetes mellitus with microalbuminuria; or
- (v) Diabetes mellitus and age 60 years of more; or
- (vi) Aboriginal or Torres Strait Islander with diabetes mellitus; or
- (vii) A Thrombolysis in Myocardial Infarction (TIMI) risk score for secondary prevention of 4 or higher

Administrative Advice:

Authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.humanservices.gov.au/HPOS).

Category / Program: GENERAL – General Schedule (Code GE)

Prescriber type: Dental Medical Practitioners Nurse practitioners Optometrists Midwives

Restriction Level / Method: Authority Required - Streamlined

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Administrative Advice: No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.
PBS indication: Non-familial hypercholesterolaemia Treatment Phase: Continuing treatment Clinical criteria: <ul style="list-style-type: none">▪ Patient must have previously received PBS-subsidised treatment with this drug for this condition AND▪ The treatment must be in conjunction with dietary therapy and exercise

7.2 Flow-on changes:

Amend the March 2019 PBAC recommended listing for alirocumab in familial heterozygous hypercholesterolaemia, as follows:

1) Permit treatment switching between evolocumab and alirocumab without the need for LDL cholesterol levels to deteriorate to levels specified in the entry criteria;

2) Prevent PBS-subsidy of combination use of evolocumab and alirocumab; the proposed text above is to replace that proposed at paragraph 8.2 of the March 2019 PSD for item 7.01;

3) Amend 'months' where it appears to 'weeks';

4) Amend '...maximum recommended dose of atorvastatin or rosuvastatin' to '...maximum recommended dose of atorvastatin (80 mg) or rosuvastatin (40 mg)...or maximum tolerated dose of atorvastatin or rosuvastatin...';

5) Amend the Authority approval method from 'In-writing only' to 'telephone/electronic' in initial and grandfather treatment and from 'telephone/electronic' to 'Streamlined' in continuing treatment for consistency with the recommended authority approval methods specified for evolocumab at the November 2019 PBAC meeting; various administrative notes and Prescriber instructions are to be revised to align with those used for evolocumab to facilitate the change from 'in-writing only' to 'telephone/electronic' authority approval;

6) Amend the LDL-c eligibility threshold in the initial/grandfather treatment restriction from 3.3 mmol/L to 2.6 mmol/L (in the presence of symptomatic atherosclerotic cardiovascular disease) for consistency with evolocumab;

7) Amend the Prescriber Instruction that defines symptomatic atherosclerotic cardiovascular disease in initial and grandfather treatment to match the edited definition recommended for evolocumab at the November 2019 PBAC meeting (shown above);

8) Remove the clinical criterion that 'Patient must commence initial treatment on a dose of 75 mg per fortnight or 300 mg per month', given that initial treatment excludes prescribing by non-specialist physicians (where dose awareness may be lower); and

9) Amend relevant references to the 'Department of Human Services' to 'Services Australia'

7.3 Amend the November 2019 PBAC recommended listing for evolocumab in non-familial hypercholesterolaemia listings, at the same time alirocumab is listed for non-familial hypercholesterolaemia, to:

- 1) Permit treatment switching between evolocumab and alirocumab without the need for LDL cholesterol levels to deteriorate to levels specified in the entry criteria; and
- 2) Prevent PBS-subsidy of combination use of evolocumab and alirocumab

7.4 Amend the existing PBS listing for evolocumab in familial heterozygous hypercholesterolaemia, at the same time alirocumab is listed for familial heterozygous hypercholesterolaemia, to:

- 1) Permit treatment switching between evolocumab and alirocumab without the need for LDL cholesterol levels to deteriorate to levels specified in the entry criteria; and
- 2) Prevent PBS-subsidy of combination use of evolocumab and alirocumab

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

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

The sponsor had no comment.