

## 6.03 EVOLOCUMAB, Injection 140 mg in 1 mL single use pre-filled pen, Injection 420 mg in 3.5 mL single use pre-filled cartridge, Repatha<sup>®</sup>, Amgen Australia Pty Ltd.

### 1 Purpose of submission

- 1.1 The Category 2 submission requested an extension of the Section 85 (Authority Required) PBS listings of evolocumab for the treatment of atherosclerotic cardiovascular disease (ASCVD) with high risk factors (including familial hypercholesterolaemia, FH) to include patients who have an LDL-C level between 1.8 and 2.6 mmol/L, despite optimised treatment with statins and ezetimibe. The submission also continued the request from previous submissions (July 2019, November 2019, November 2020 PBAC meetings) to allow general practitioners (GPs) to initiate evolocumab in consultation with a specialist.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus placebo (optimised background treatment).

**Table 1: Key components of the clinical issue addressed in the submission (as stated in the submission)**

Component	Description
Population	Patients with ASCVD and high-risk factors (including familial hypercholesterolaemia) and LDL-C > 1.8 and ≤ 2.6 mmol/L despite maximal tolerated statins and ezetimibe.
Intervention	Evolocumab 140 mg every two weeks or 420 mg every month, administered by subcutaneous injection
Comparator	Placebo
Outcomes	Reduction in LDL-C and major cardiovascular events
Clinical claim	Evolocumab is superior to placebo in terms of comparative efficacy and similar in terms of comparative safety

Source: Table 1.1-1, p11 of the submission.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL-C, low density lipoprotein cholesterol.

### 2 Background

#### **Registration status**

- 2.1 Evolocumab was first registered by the TGA in December 2015 for treatment of primary hypercholesterolaemia and homozygous familial hypercholesterolaemia. The TGA indication was later revised in August 2018 to include the prevention of cardiovascular events.
- 2.2 At the time of this submission, the TGA approved indication for evolocumab was:
- to reduce the risk of cardiovascular events (myocardial infarction, stroke, and coronary revascularisation) in adults with established cardiovascular disease in combination with an optimally dosed statin and/or other lipid-lowering therapies

- for the treatment of adults with primary hypercholesterolaemia (including heterozygous familial hypercholesterolaemia and non-familial hypercholesterolaemia) to reduce low-density lipoprotein cholesterol:
  - in combination with a statin or statin with other lipid lowering therapies, or
  - alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant
- for the treatment of adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid lowering therapies.

***Previous PBAC consideration***

- 2.3 At the time of this submission, evolocumab had PBS listings for homozygous FH, heterozygous FH, and non-FH with ASCVD and additional risk factors. To be eligible for PBS subsidy:
- Patients with homozygous FH must have LDL-C levels above 2.6 mmol/L despite optimised treatment with statins (if tolerated/not contraindicated).
  - Patients with heterozygous FH must have LDL-C above 2.6 mmol/L in the presence of symptomatic ASCVD, or above 5.0 mmol/L, despite optimised treatment with statins (if tolerated/not contraindicated) and ezetimibe.
  - Patients with non-FH with symptomatic ASCVD and additional risk factors must have LDL-C above 2.6 mmol/L despite optimised treatment with statins (if tolerated/not contraindicated) and ezetimibe.
- 2.4 A summary of recent PBAC considerations of evolocumab relevant to the current submission is presented in Table 2 below.

**Table 2: Summary of relevant recent PBAC considerations of evolocumab**

Submission	Requested listing	PBAC decision
July 2019	Non-FH with ASCVD and additional risk factors and LDL-C > 2.6 mmol/L Extension of listing for FH to include patients with ASCVD who have LDL-C between 2.6 and 3.3 mmol/L Treatment criterion to permit GP prescribing for initial use in consultation with specialist	Deferred recommendation for non-FH, considering the ICER was high and a price reduction was required to bring the ICER into an acceptable range. Also deferred recommendation for extended LDL-C range for FH, but the PBAC considered that these patients would have at least an equivalent lifetime risk to the non-FH population. Should evolocumab be considered cost-effective in the non-FH population, the cost-effectiveness of evolocumab for an expanded FH listing could be inferred at the same price as for non-FH.
November 2019	Minor changes to July 2019 proposed listing as suggested by PBAC. Revised model, including a reduced price to achieve an ICER of less than \$25,000 to < \$35,000, and updated financial estimates. Continued request to allow GPs to initiate treatment in consultation with a specialist.	Recommended for non-FH patients with ASCVD who have LDL-C > 2.6 mmol/L and additional risk factors; and FH in patients with symptomatic ASCVD or HoFH, who have LDL-C between 2.6 and 3.3 mmol/L. PBAC recommended that the treatment criterion for initiation of evolocumab should remain 'Must be treated by a specialist physician'.
November 2020	Requested change to all existing initial listings to allow GPs to initiate treatment in consultation with a specialist.	The PBAC did not recommend the amendment to listings, citing several concerns with expanding prescriber types after the evolocumab listing had just been updated 5 months prior (in May 2020): <ul style="list-style-type: none"> <li>- Evolocumab is a relatively new drug with uncertain uptake and financial estimates;</li> <li>- Evolocumab is a (novel) third-line therapy, with only 20% of GPs regularly prescribing second-line therapies;</li> <li>- Whilst there is an RSA in place, there is still the risk of use outside the intended high-risk population (particularly for non-familial hypercholesterolaemia);</li> <li>- There is also the risk of patients undergoing inadequate trials of statin therapy before commencing treatment with evolocumab.</li> </ul> The PBAC advised it would be appropriate for DJSC to review utilisation data after at least 18 months from the date that the non-FH listing was added, and the issue of GP initiation could be reassessed at that time.

Source: evolocumab Public Summary Document (PSD), July 2019 PBAC meeting; evolocumab PSD, November 2019 PBAC meeting; evolocumab PSD, November 2020 PBAC meeting.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; GP, general practitioner; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL, low density lipoprotein cholesterol; RSA, risk sharing arrangement.

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

### 3 Requested listing

3.1 The submission's proposed changes to the existing initial restriction for non-FH with ASCVD are presented below using strikethrough for proposed deletions and underline for proposed additions. The same changes were requested for both the homozygous familial hypercholesterolaemia (HoFH) and heterozygous familial hypercholesterolaemia (HeFH) initial listings. Lower published and effective prices

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were proposed, which would apply across all evolocumab PBS item codes. No changes to the evolocumab continuing treatment listings were requested other than the change in price.

Name, Restriction, Manner of administration and form	Max. Qty (units)	No. of Rpts	Dispensed Price for Max. Qty Published (Effective <sup>a</sup> )	Proprietary Name and Manufacturer
EVOLOCUMAB, 140 mg/mL injection, 1 mL injection device	2	5	(\$ )	Repatha® Amgen
EVOLOCUMAB, 140 mg/mL injection, 1 mL injection device	3 <sup>b</sup>	5	(\$ )	
EVOLOCUMAB, 420 mg/mL injection, 3.5 mL injection device	1	5	(\$ )	

<sup>a</sup> Effective price is for the extended population only (LDL-C > 1.8 and ≤ 2.6 mmol/L).

<sup>b</sup> Applies to the homozygous familial hypercholesterolaemia listing only; effective price calculated during the evaluation to adjust for maximum quantity of 3.

<b>Category / Program:</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	Medical Practitioners
<b>PBS Indication:</b>	Non-familial hypercholesterolaemia
<b>Treatment phase:</b>	Initial treatment
<b>Restriction:</b>	Authority Required – Telephone/Emergency/Electronic
<b>Clinical criteria:</b>	<ul style="list-style-type: none"> <li>• The treatment must be in conjunction with dietary therapy and exercise, AND</li> <li>• Patient must not be receiving concomitant PBS-subsidised treatment with another drug that belongs to the same pharmacological class as this drug, AND</li> <li>• Patient must have symptomatic atherosclerotic cardiovascular disease, AND</li> <li>• Patient must have an LDL cholesterol level in excess of <del>2.6</del> <u>1.8</u> millimoles per litre, AND</li> <li>• Patient must have atherosclerotic disease in two or more vascular territories (coronary, cerebrovascular or peripheral vascular territories); OR</li> <li>• Patient must have severe multi-vessel coronary heart disease defined as at least 50% stenosis in at least two large vessels; OR</li> <li>• 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</li> <li>• Patient must have diabetes mellitus with microalbuminuria; OR</li> <li>• Patient must have diabetes mellitus and be aged 60 year or more; OR</li> <li>• Patient must be an Aboriginal or Torres Strait Islander with diabetes mellitus; OR</li> <li>• Patient must have a Thrombolysis in Myocardial Infarction (TIMI) risk score for secondary prevention of 4 or higher AND</li> <li>• Patient must have been treated with the maximum recommended dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily) 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</li> <li>• Patient must have developed clinically important product-related adverse events necessitating withdrawal of statin treatment to trials of each of atorvastatin and rosuvastatin; OR</li> <li>• Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information, AND</li> <li>• Patient must have been treated with ezetimibe for at least 12 consecutive weeks in conjunction with a statin (if tolerated), dietary therapy and exercise.</li> </ul>
<b>Treatment criteria:</b>	Must be treated by or in consultation with a specialist physician

<p><b>Prescriber Instructions:</b></p>	<p>Symptomatic atherosclerotic cardiovascular disease is defined as:</p> <ul style="list-style-type: none"> <li>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</li> <li>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</li> <li>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)).</li> </ul> <p>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.</p> <p>A clinically important product-related adverse event is defined as follows:</p> <ul style="list-style-type: none"> <li>i. Severe myalgia (muscle symptoms without creatine kinase elevation) which is proven to be temporally associated with statin treatment; or</li> <li>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</li> <li>iii. Unexplained, persistent elevations of serum transaminases (greater than 3 times the upper limit of normal) during treatment with a statin.</li> </ul> <p>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 retrial should occur after a washout period of at least 4 weeks, or if the creatine kinase (CK) level is elevated, retrial should not occur until CK has returned to normal.</p> <p>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.</p> <p>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> <ul style="list-style-type: none"> <li>(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</li> <li>(ii) the doses, duration of treatment and details of adverse events experienced with trials with each of atorvastatin and rosuvastatin; or</li> <li>(iii) the patient is contraindicated to treatment with a statin as defined in the TGA-approved Product Information.</li> </ul> <p>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:</p> <ul style="list-style-type: none"> <li>(i) atherosclerotic disease in two or more vascular territories (coronary, cerebrovascular or peripheral vascular territories); or</li> <li>(ii) severe multi-vessel coronary heart disease defined as at least 50% stenosis in at least two large vessels; or</li> </ul>
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	<ul style="list-style-type: none"> <li>(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</li> <li>(iv) diabetes mellitus with microalbuminuria; or</li> <li>(v) diabetes mellitus and age 60 years of more; or</li> <li>(vi) Aboriginal or Torres Strait Islander with diabetes mellitus; or</li> <li>(vii) Thrombolysis in Myocardial Infarction (TIMI) risk score for secondary prevention of 4 or higher</li> </ul>
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- 3.2 The submission also requested grandfather listings for evolocumab for non-FH and HeFH to allow transfer to PBS-subsidised treatment for patients who may be self-funding evolocumab or who have participated in an evolocumab clinical trial and who meet the expanded PBS eligibility criteria.
- 3.3 The submission broadened the qualifying LDL-C threshold from 2.6 mmol/L used in previous submissions, to a 1.8 mmol/L threshold. The submission justified the revised threshold based on international clinical guidelines. The evaluation noted that the guidelines cited in the submission are consistent with older treatment guidelines, which have also generally recommended a lower target LDL-C threshold of 1.8 mmol/L in patients with atherosclerotic disease. It was further noted that higher thresholds have been nominated historically in order to identify populations most likely to benefit from LDL-C reductions given the high cost of PCSK9 inhibitors; however, the ESC considered the requested change may be supported if cost-effectiveness in the lower risk population was acceptable.
- 3.4 The submission also included a request to allow initiation of evolocumab by GPs in consultation with a specialist. The submission noted that by the time of the July 2022 PBAC meeting, 27 months will have elapsed from the most recent listing amendment, for evolocumab, which is longer than the 18-month minimum period the PBAC stated was necessary before it reconsidered its request (para 5.6, evolocumab Public Summary Document (PSD), November 2020 PBAC meeting). At the November 2020 meeting, the PBAC had several other concerns with expanding the prescriber types after the listing for evolocumab had been updated just 5 months prior to include patients with non-FH with ASCVD and other risk factors; none of these issues were directly addressed in the current submission (see Table 2 above). The Pre-Sub-Committee Response (PSCR) commented that it expects evolocumab prescriptions to be initiated by the small, experienced group of GPs who regularly prescribe second-line cardiovascular therapies, that these GPs are unlikely to prescribe a novel injectable therapy without specialist consultation, and that it is unclear why risks of use outside the restriction would be greater with GP initiation than with specialists. The ESC considered that the previous issues remain, but that retaining a Telephone/Electronic Authority may help to mitigate risk of substantial leakage outside the eligible population. The DUSC noted that evolocumab was no longer a novel agent.
- 3.5 In a recent analysis of evolocumab utilisation by the Drug Utilisation Sub-Committee, DUSC commented that there is a lag in predicted versus actual reviews due to data processing, and as the non-familial listing was added to the PBS 1 May 2020, it would

be due for DUSC review at the February 2023 meeting at the earliest (p25, Evolocumab for heterozygous familial hypercholesterolaemia: predicted versus actual analysis, DUSC report, June 2021).

- 3.6 The submission noted that the current PBS listings for evolocumab at the time of the submission (March 2022) were subject to a special pricing arrangement (SPA) consisting of a % rebate on government expenditure. In April 2022 there was a 5% statutory price reduction for evolocumab, reducing both published and the effective prices, and the SPA rebate level was maintained.
- 3.7 In the current submission, the sponsor proposed a further reduced published DPMQ. Maintaining the same effective price (\$) for the existing population (with LDL-C > 2.6 mmol/L) reduced the rebate to % (on the new lower published DPMQ) for these patients.
- 3.8 The effective DPMQ for the new population (\$) with LDL-C > 1.8 and ≤ 2.6 mmol/L was based on the evolocumab price required to achieve an incremental cost per additional QALY of \$25,000 to < \$35,000 in the submission’s economic evaluation. This was adjusted to \$ for the 140 mg dose (to adjust for 28-day supply). The weighted rebate between dose strengths was calculated at % based on assumption of 80% use of the 140 mg dose, and 20% for 420 mg. The PSCR presented an analysis which adjusted the baseline mean LDL-C level, resulting in an incremental cost per additional QALY of \$25,000 to < \$35,000 (see paragraph 6.33).
- 3.9 Weighting between the current and new populations was derived by combining the agreed total services for the existing risk sharing arrangement with the submission’s forecast services for the new population. The submission stated that peak uptake was assumed to be reached in 2024, when the existing population was estimated to represent % (400,000 to < 500,000 scripts) of the total uptake, and % for the new population (100,000 to < 200,000 scripts). The submission’s proposed overall weighted rebate (from the new published DMPQ) is % (i.e., x % + x %), resulting in an effective weighted DPMQ of \$ (140 mg injection) and \$ (420 mg injection). The proposed price changes are summarised in Table 3. Detailed calculations were presented in Attachment 1.4 of the commentary.

**Table 3: Proposed changes to published and effective prices**

	Rebate	Published Price (DPMQ)		Effective Price (DPMQ)	
		140 mg	420 mg	140 mg	420 mg
Pricing at Feb 2022	%	\$497.88	\$539.18	\$	\$
Pricing at April 2022	%	\$473.32	\$512.57	\$	\$
Existing population, lower published price	%	\$	\$	\$	\$
New population, lower published and effective price	%	\$	\$	\$	\$
Weighted price (existing/new population)	%	\$	\$	\$	\$

Source: Table 1.4-5, p27 of the submission 'Price and cap calculations' Excel spreadsheet, Appendix 6 of the submission

Abbreviations: DPMQ, dispensed price for maximum quantity.

Note: for simplicity, the DPMQ for evolocumab 140 mg is based on the maximum quantity of 2. Similar price reductions were proposed for the homozygous familial hypercholesterolaemia listing, which has a maximum quantity of 3.

- 3.10 The weighting between current and new populations and the consequent weighted effective price is dependent on the size of the eligible patient population and the assumed uptake of evolocumab in patients with LDL-C between 1.8 and 2.6 mmol/L. Given the uncertainties regarding the submission's estimated size of the eligible population and uptake assumptions, the evaluation considered that the calculated weighted effective price may not be appropriate. The PSCR maintained the face validity of lower uptake rates in patients with LDL-C levels closer to the target of < 1.8 mmol/L. To support this claim, the PSCR presented a 2022 chart audit conducted by the sponsor in the United States (US), in which 12% of patients (155/1,286) had an LDL-C below 2.6 mmol/L prior to initiating a PCSK9 inhibitor. The ESC noted that this data could not be verified, that no information was provided with respect to eligibility requirements for treatment or background therapies and that it was unclear what proportion of patients with symptomatic ASCVD had LDL-C below 2.6 mmol/L. Overall, the US data was of unknown applicability to the Australian population. The ESC considered that the assumption of higher uptake in the existing population compared with the expanded population met face validity, but that the split (1%/1%) was highly uncertain.
- 3.11 The pre-PBAC provided a revised price proposal, which it stated reflected an increase in the weighting of the additional population from 1% to 1%. The pre-PBAC response then stated the assumed population distribution for pricing purposes would effectively be 1% FH: 1% ASCVD > 2.6 mmol/L: 1% ASCVD > 1.8 and ≤ 2.6 mmol/L.

**Table 4: Revised price proposal**

Price basis	Rebate	140 mg in 1 mL pen device <sup>a</sup>		420 mg in 3.5 mL cartridge	
		Published DPMQ <sup>b</sup>	Effective DPMQ <sup>b</sup>	Published DPMQ <sup>b</sup>	Effective DPMQ <sup>b</sup>
Existing listing prices					
April 2022 prices (inc. 5% SPR)	% <sup>c</sup>	\$473.32	\$	\$512.57	\$
With a further reduction in published price	% <sup>d</sup>	\$	\$	\$	\$
Proposed prices – additional population	%	\$	\$	\$	\$
Submission overall weighted prices	%	\$	\$	\$	\$
Revised overall weighted prices	%	\$	\$	\$	\$

Abbreviations: DPMQ = dispensed price for maximum quantity; SPR = statutory price reduction.

a. For simplicity, only prices for the maximum quantity of 2 are shown.

b. Based on supply chain cost, fees and co-payments current as of June 2022.

c. Current deed rebate.

d. Revised rebate for existing listing with further reduction of list price, keeping effective prices the same.

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

## 4 Population and disease

- 4.1 Hypercholesterolaemia is a common condition characterised by elevated serum cholesterol levels. The causes of hypercholesterolaemia can include both genetic and environmental factors (e.g., diet and lifestyle). The vast majority of patients with hypercholesterolaemia have elevated cholesterol levels in the absence of any specific genetic disorder.
- 4.2 Hypercholesterolaemia is associated with the development of atherosclerosis and an increased incidence of myocardial infarction, stable or unstable angina, coronary revascularisation procedures, stroke, transient ischaemic attack, carotid endarterectomy and intermittent claudication of peripheral arteries. These cardiovascular events can have a major impact on survival, quality of life and the future risk of further cardiovascular events.
- 4.3 Evolocumab is a monoclonal antibody that binds to circulating PCSK9 enzyme (proprotein convertase subtilisin/kexin type 9) which prevents PCSK9-mediated degradation of low-density lipoprotein receptors (LDLR) on the surface of hepatic cells. Up-regulation of LDLR is associated with decreased serum LDL-C cholesterol levels.
- 4.4 The submission positioned evolocumab as a treatment option in patients with LDL-C levels above 1.8 mmol/L despite optimised treatment with statins and ezetimibe; (patients with HoFH need only to have trialled optimised treatment with statins).

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

## 5 Comparator

- 5.1 The submission claimed that evolocumab would be used in addition to optimised background treatment (with statins and ezetimibe) and therefore nominated

‘placebo’ (optimised background treatment) as the main comparator, noting that the PBAC has considered ‘placebo’ an appropriate comparator in previous evaluations of evolocumab, most recently at the July 2019 and November 2019 PBAC meetings. This comparator was appropriate.

- 5.2 The submission noted that alirocumab, a PCSK9 inhibitor from the same class as evolocumab, is listed on the PBS with the same restrictions as evolocumab. The sponsor did not consider alirocumab in this submission as a dose relativity between evolocumab and alirocumab has already been established.
- 5.3 The submission also noted that inclisiran, another PCSK9 inhibitor with a different mechanism of action to evolocumab, is TGA registered but not PBS listed in Australia, and was not included in the current submission due to the current lack of cardiovascular outcomes data for inclisiran. While inclisiran is not a relevant comparator for this submission, there may be flow on consequences for any future PBAC consideration of inclisiran (a submission for July 2021 PBAC consideration was withdrawn).

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician highlighted that evolocumab was an important treatment option for highest risk patients, described how LDL-C targets have reduced over the past decade, and explained that there are many patients with LDL-C levels between 1.8 and 2.6 mmol/L who have significant cardiovascular disease and would benefit from treatment with evolocumab or alirocumab. The clinician described how evolocumab is well tolerated, with manageable injection reactions. The clinician was also supportive of extending initial prescribing to GPs in consultation with a speciality, noting that GPs currently play an important role in continuing therapy. The clinician considered that there was currently underutilisation of this treatment particularly among high-risk patients who require aggressive LDL-C reduction. The PBAC noted the clinical perspective was supportive of the requested broader access to evolocumab.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (2), health care professionals (13) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described how the proposed expanded listing would be in line with international clinical guidelines, and would be expected to reduce a range of cardiovascular events. Evolocumab was considered well tolerated. One individual commented that the lack of eligibility under current PBS criteria had resulted in a significant financial burden on their household. The vast majority of comments were supportive of GP initiation in consultation with specialists, noting current

underutilisation resulting from limited access to specialists.

- 6.3 The PBAC noted the advice received from Hearts4heart, which described patient viewpoints of using evolocumab. The patients expressed the peace of mind they felt knowing that they were doing something to reduce their risk of cardiovascular events. The injectable formulation was considered manageable. Hearts4heart also supported initial GP prescribing in order to broaden treatment access, since initiation by specialist physicians could require long wait times. Specialist initiation raised equity issues for patients outside major urban centres, for patients with lower socio-economic status or poor mental health, as well as for older Australians and Aboriginal and/or Torres Strait Islander populations.
- 6.4 The PBAC also noted input from Her Heart, which was supportive of the expanded LDL-C criteria and GP initiation in consultation with specialists, noting that the restriction to specialist initiation posed equity issues, which further exacerbated gender disparities in relation to prescribing and adherence to treatment.
- 6.5 The PBAC noted that comments were supportive of the arguments provided in the submission for broader access to evolocumab.

### **Clinical trials**

- 6.6 The submission was based on one head-to-head comparison of cardiovascular outcomes with evolocumab versus placebo in hypercholesterolaemia patients with atherosclerotic cardiovascular disease (FOURIER). Data from the FOURIER trial has been considered previously by the PBAC.
- 6.7 The submission did not present specific clinical data to support the proposed extension of listing for hypercholesterolaemia patients with atherosclerotic disease who have an LDL-C level between 1.8 and 2.6 mmol/L, however patients with baseline LDL-C within this range were included in the FOURIER trial.
- 6.8 Details of the trial presented in the submission are provided in Table 5 below.

**Table 5: Trial and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
FOURIER	A Double-blind, Randomised, Placebo-controlled, Multicenter Study Assessing the Impact of Additional LDL-Cholesterol Reduction on Major Cardiovascular Events When Evolocumab (AMG 145) is Used in Combination With Statin Therapy in Patients with Clinically Evident Cardiovascular Disease.	Clinical Study Report, 10 April 2017
	Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease.	<i>NEJM</i> 2017; 376 (18): 1713-1722
	Sabatine MS, De Ferrari GM, Giugliano RP, et al. Clinical benefit of evolocumab by severity and extent of coronary artery disease.	<i>Circulation</i> 2018; 138 (8): 756-766

Source: Table 2.1-1, p29 of the submission.

- 6.9 The key features of the FOURIER trial are summarised in Table 6.

**Table 6: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
FOURIER	27,564	MC, R, DB, PC Median 2.2 year duration	Low	Hypercholesterolaemia with atherosclerotic disease and additional risk factors, despite optimised lipid lowering therapies	Cardiovascular events, lipid parameters	Used to support relationship between LDL-C and cardiovascular events

Source: Table 2.3-1, p29 of the submission; Table 1.1-1, Appendix 3 of the submission

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

6.10 Baseline LDL-C values in the evolocumab arm ranged from 0.59 mmol/L to 20.32 mmol/L (median 2.37 mmol/L), with an average of 2.532 (SD 0.748) mmol/L. In the placebo arm, baseline LDL-C ranged from 0.85 to 15.64 mmol/L (median 2.380 mmol/L), with an average of 2.529 (SD 0.703) mmol/L. The majority of patients in the FOURIER trial had baseline LDL-C levels between 1.8 and 2.6 mmol/L (approximately 1.1% of patients in each treatment arm had LDL-C lower than 1.8 mmol/L at baseline, which were noted as protocol deviations).

### ***Comparative effectiveness***

6.11 Key cardiovascular outcomes reported in the FOURIER trial are summarised in Table 7.

Table 7: Key cardiovascular time to event analyses reported in the FOURIER trial

Outcome	Evolocumab N = 13,784	Placebo N = 13,780	Hazard ratio (95% CI)
<b>Composite outcomes (first event only)</b>			
Time to cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina, or coronary revascularisation [primary outcome]	1,344 (9.75%)	1,563 (11.34%)	<b>0.85 (0.79, 0.92)</b>
Time to cardiovascular death, myocardial infarction, or stroke	816 (5.92%)	1,013 (7.35%)	<b>0.80 (0.73, 0.88)</b>
Time to cardiovascular death or first hospitalisation for worsening heart failure	402 (2.92%)	408 (2.96%)	0.98 (0.86, 1.13)
Time to first ischaemic stroke or transient ischaemic attack	229 (1.66%)	295 (2.14%)	<b>0.77 (0.65, 0.92)</b>
CTTC composite (coronary death, myocardial infarction, stroke or coronary revascularisation) [post hoc outcome]	1,271 (9.22%)	1,512 (10.97%)	<b>0.83 (0.77, 0.90)</b>
<b>Individual outcomes</b>			
Time to cardiovascular death	251 (1.82%)	240 (1.74%)	1.05 (0.88, 1.25)
- Death due to myocardial infarction	25 (0.18%)	30 (0.22%)	0.84 (0.49, 1.42)
- Death due to stroke	31 (0.22%)	33 (0.24%)	0.94 (0.58, 1.54)
- Death due to other cardiovascular causes	195 (1.41%)	177 (1.28%)	1.10 (0.90, 1.35)
Time to coronary death	176 (1.28%)	173 (1.26%)	1.02 (0.82, 1.25)
Time to death by any cause	444 (3.22%)	426 (3.09%)	1.04 (0.91, 1.19)
Time to first myocardial infarction	468 (3.40%)	639 (4.64%)	<b>0.73 (0.65, 0.82)</b>
Time to first stroke	207 (1.50%)	262 (1.90%)	<b>0.79 (0.66, 0.95)</b>
- Ischaemic stroke	171 (1.24%)	226 (1.64%)	<b>0.75 (0.62, 0.92)</b>
- Haemorrhagic stroke	29 (0.21%)	25 (0.18%)	1.16 (0.68, 1.98)
- Unknown	13 (0.09%)	14 (0.10%)	0.93 (0.44, 1.97)
Time to first coronary revascularisation	759 (5.51%)	965 (7.00%)	<b>0.78 (0.71, 0.86)</b>
- Urgent procedure	403 (2.92%)	547 (3.97%)	<b>0.73 (0.64, 0.83)</b>
- Elective procedure	420 (3.05%)	504 (3.66%)	<b>0.83 (0.73, 0.95)</b>
Time to first hospitalisation for unstable angina	236 (1.71%)	239 (1.73%)	0.99 (0.82, 1.18)
Time to first hospitalisation for worsening heart failure	194 (1.41%)	201 (1.46%)	0.96 (0.79, 1.17)

Source: Table 1.3-1, Appendix 3 of the submission.

Abbreviations: CTTC, Cholesterol Treatment Trialists' Collaboration

**Bold** indicates statistically significant results

- 6.12 Treatment with evolocumab was associated with a statistically significant decreased risk of cardiovascular events compared to placebo. Disaggregated cardiovascular outcomes indicate that treatment with evolocumab was associated with a decreased risk of myocardial infarction, coronary revascularisation and ischaemic stroke compared to placebo. There was no apparent difference in angina, coronary death, cardiovascular death, or all-cause mortality between treatment arms.
- 6.13 The submission noted that the benefits of evolocumab were largely consistent across major subgroups, including those based on disease severity, baseline risk and comorbidities. Results were also consistent across baseline LDL-C quartiles for the primary and key secondary endpoints (see Table 8). The benefit of evolocumab was also consistent across levels of intensity of statin therapy, irrespective of ezetimibe use or evolocumab dose regimen.

**Table 8: Relationship between LDL-C levels and cardiovascular outcomes from the FOURIER trial**

LDL-C measures	Evolocumab	Placebo	Primary composite CV outcome <sup>a</sup> HR (95% CI)	Secondary composite CV outcome <sup>b</sup> HR (95% CI)
<b>Baseline LDL-C Quartile 1, &lt; 79.5 mg/dL [2.1 mmol/L] (N = 6,961)</b>				
Baseline LDL-C mmol/L, mean (SE)	1.86 (0.003)	1.86 (0.003)	<b>0.80</b> (0.68, 0.93)	<b>0.78</b> (0.64, 0.95)
Endpoint LDL-C mmol/L, mean (SE), Week 48	0.74 (0.010)	1.98 (0.010)		
Change LDL-C mmol/L, mean (SE), Week 48	-1.11 (0.010)	0.12 (0.010)		
Change LDL-C % reduction, mean (SE), Week 48	-59.67 (0.61)	6.49 (0.52)		
<b>Baseline LDL-C Quartile 2, &gt; 79.5 mg/dL [2.1 mmol/L] to &lt; 91.5 mg/dL [2.4 mmol/L] (N = 6,886)</b>				
Baseline LDL-C mmol/L, mean (SE)	2.22 (0.003)	2.22 (0.003)	<b>0.83</b> (0.71, 0.96)	<b>0.80</b> (0.66, 0.97)
Endpoint LDL-C mmol/L, mean (SE), Week 48	0.86 (0.013)	2.25 (0.010)		
Change LDL-C mmol/L, mean (SE), Week 48	-1.34 (0.013)	0.03 (0.010)		
Change LDL-C % reduction, mean (SE), Week 48	-60.51 (0.56)	1.52 (0.43)		
<b>Baseline LDL-C Quartile 3, 91.5 mg/dL [2.4 mmol/L] to &lt; 108.5 mg/dL [2.8 mmol/L] (N = 6,887)</b>				
Baseline LDL-C mmol/L, mean (SE)	2.57 (0.003)	2.57 (0.003)	0.89 (0.77, 1.03)	<b>0.79</b> (0.66, 0.94)
Endpoint LDL-C mmol/L, mean (SE), Week 48	1.01 (0.013)	2.53 (0.010)		
Change LDL-C mmol/L, mean (SE), Week 48	-1.56 (0.013)	-0.05 (0.010)		
Change LDL-C % reduction, mean (SE), Week 48	-60.85 (0.54)	-1.74 (0.43)		
<b>Baseline LDL-C Quartile 4, &gt; 108.5 mg/dl [2.8 mmol/L] (N = 6,829)</b>				
Baseline LDL-C mmol/L, mean (SE)	3.50 (0.016)	3.46 (0.013)	0.89 (0.77, 1.02)	<b>0.84</b> (0.70, 0.99)
Endpoint LDL-C mmol/L, mean (SE), Week 48	1.47 (0.021)	3.18 (0.018)		
Change LDL-C mmol/L, mean (SE), Week 48	-2.03 (0.021)	-0.28 (0.016)		
Change LDL-C % reduction, mean (SE), Week 48	-58.45 (0.54)	-7.52 (0.47)		

Source: Figures 1.3-4 and 1.3-5, Appendix 3 of the submission, Table 14-4.18.15 (pp1045-1075) of the FOURIER trial report

Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio; LDL, low density lipoprotein cholesterol; SE, standard error

**Bold** indicates statistically significant results

<sup>a</sup> The primary outcome was the time to cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina, or coronary revascularisation

<sup>b</sup> The secondary outcome was the time to cardiovascular death, myocardial infarction, or stroke

### **Comparative harms**

- 6.14 The overall incidence of adverse events in the FOURIER trial was similar in both the evolocumab and placebo treatment arms. The most frequently reported adverse events (> 2% of patients) in both treatment arms were diabetes mellitus, nasopharyngitis, upper respiratory tract infection, back pain, arthralgia, urinary tract infection, bronchitis, myalgia, dizziness, influenza, diarrhoea, pneumonia, atrial fibrillation, and muscle spasms.
- 6.15 Regarding adverse events of special interest, treatment with evolocumab was associated with a higher incidence of mild to moderate hypersensitivity reactions and injection site reactions.
- 6.16 The development of anti-evolocumab antibodies was detected in a small number of patients. The presence of anti-evolocumab antibodies was not associated with a reduction in treatment efficacy or an increase in the incidence of adverse events.
- 6.17 No new safety concerns were identified in the most recent Periodic Safety Update Report for evolocumab covering the period from July 2020 to July 2021.

### **Benefits/harms**

- 6.18 On the basis of direct evidence presented in the submission, for every 1,000 hypercholesterolemia patients with atherosclerotic disease and additional risk factors with LDL-C  $\geq$  1.8 mmol/L who are treated with evolocumab plus optimal care with statins and ezetimibe in comparison to ‘placebo’ plus optimal care with statins and ezetimibe would result in:
- Approximately 60% lower LDL-C levels over a mean duration of 2 years.
  - Approximately 12 fewer patients with myocardial infarction over a mean duration of 2 years.
  - Approximately 4 fewer patients with ischaemic stroke over a mean duration of 2 years.
  - Approximately 15 fewer patients with coronary revascularisation over a mean duration of 2 years.
  - No apparent difference in cardiovascular death over a mean duration of 2 years.
  - No apparent difference in adverse events over a mean duration of 2 years.
- 6.19 No data were presented specifically for the subgroup of patients with LDL-C between 1.8 and 2.6 mmol/L.

### **Clinical claim**

- 6.20 The submission claimed that evolocumab (plus optimised background treatment) is superior to ‘placebo’ (optimised background treatment) in terms of comparative efficacy and similar in terms of comparative safety in patients with familial hypercholesterolaemia or non-familial hypercholesterolaemia with ASCVD and risk factors, who have LDL-C levels between 1.8 and 2.6 mmol/L. This claim was previously accepted as reasonable by the PBAC for the patient population with LDL-C levels above 2.6 mmol/L, based on the same clinical data. The ESC noted that the same proportional benefit was expected to be achieved across different LDL-C percentile ranges (see Table 8 above), with lower absolute treatment benefit expected due to lower baseline risk in the proposed additional patient group.
- 6.21 The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.22 The PBAC considered that the claim of similar comparative safety was reasonable.

### **Economic analysis**

- 6.23 The submission presented a stepped economic evaluation of evolocumab for the treatment of non-familial hypercholesterolaemia patients with atherosclerotic disease and additional risk factors, who have an LDL-C level between 1.8 and 2.6 mmol/L despite optimised treatment with statins and ezetimibe. The economic evaluation was based on relative LDL reductions from the FOURIER trial and other modelled variables. The economic evaluation was presented as a cost-effectiveness/cost-utility analysis.

- 6.24 An economic evaluation of the expanded population in familial hypercholesterolaemia was not presented, but the PBAC previously considered that, should evolocumab be considered cost-effective in the non-FH population, then the cost-effectiveness of evolocumab could be inferred for an expanded FH listing, at the same price as accepted for non-FH (para 3.4, evolocumab PSD, November 2019 PBAC meeting).
- 6.25 The submission stated that the economic model was essentially unchanged from that presented with the July 2019 evolocumab submission for non-familial hypercholesterolaemia patients with atherosclerotic disease and additional risk factors as an add-on to existing therapies; this was later refined in the November 2019 evolocumab submission. Between July 2019 and November 2019, the model was revised with: a lower price; a shorter time horizon (25 years versus 35 years); a modified cardiovascular mortality lag (3.6 years versus a lag of 2 years with linear adjustment for 2 years); cardiovascular event rates and distribution of cardiovascular events based on FOURIER trial data rather than Swedish registry data; the introduction of a treatment discontinuation rate of 1% per cycle for the first 4 years; and a correction to the magnitude of difference in baseline LDL-C between FOURIER and the proposed PBS population from 0.93 to 0.8 mmol/L (para 6.48, evolocumab PSD, July 2019 PBAC meeting; para 4.3, evolocumab PSD, November 2019 PBAC meeting).
- 6.26 The only changes between models presented in November 2019 and the current submission were: a lower price for evolocumab, changed average baseline LDL-C level and the associated annual cardiovascular event rate of the additional population with lower LDL-C levels. The steps applied in the model to move from the previously accepted population in November 2019 to the proposed new population are outlined in Table 9 below.

**Table 9: Key differences in economic analysis between November 2019 and July 2022 submissions**

Variable	November 2019 submission	July 2022 submission
Mean baseline LDL-C (mmol/L)	3.3 mmol/L (based on FOURIER individual patient data with LDL-C > 2.6 mmol/L threshold)	2.325 mmol/L (based on sponsor-commissioned study of GP records and assumed uptake in the population with LDL-C > 1.8 and ≤ 2.6 mmol/L)
Difference in LDL-C between PBS and FOURIER populations (mean 2.5 mmol/L)	+0.8 mmol/L	-0.175 mmol/L
CHD event rate/year for untreated patients <sup>a</sup>	$(0.042 \times 1.35 / 0.78^{0.8}) = 0.069$	$(0.042 \times 1.35 / 0.78^{-0.175}) = 0.054$
Evolocumab cost/month required to achieve ICER of \$25,000 to < \$35,000/year	\$	\$

Source: Constructed during the evaluation

Abbreviations: CHD, coronary heart disease; CTTC, Cholesterol Treatment Trialists' Collaboration; GP, general practitioner; LDL-C, low density lipoprotein cholesterol

<sup>a</sup> 0.042 is the observed CHD event rate in FOURIER; 1.35 is the hazard ratio for events in the requested high risk patient population compared with patients in FOURIER, based on a comparison of baseline risk in the placebo arm from each subgroup to the placebo arm of the overall study population; 0.78 is the relative risk of major vascular events associated with lowering the LDL-C in a patient population by 1 mmol/L, based on a CTTC meta-analysis; and 0.8 (Nov 2019) and -0.175 (July 2022) are the differences in mean LDL-C for the requested patient population compared with FOURIER.

6.27 Key components of the economic evaluation are presented in Table 10 below.

**Table 10: Key components of the economic evaluation**

Component	Description
Type of analysis	Cost-effectiveness analysis/cost-utility analysis
Treatments	Evolocumab, placebo
Outcomes	% reduction in LDL-C; life years; quality-adjusted life years, number of MI and IS events
Time horizon	25 years
Methods used to generate results	Markov cohort expected value analysis (with half-cycle correction)
Health states	Five health states: baseline health state (atherosclerotic disease), myocardial infarction (only ischaemic stroke (ever), cardiovascular death and non-cardiovascular death
Cycle length	Monthly
Transition probabilities	Treatment reduces LDL-C, with a consequent change in the CHD event rate estimated using the relationship reported by CTTC. CHD event rate increases with age. Distribution of the type of CHD events based on outcomes in FOURIER, with the odds of death for a CHD event increasing with age. Non-CHD death event rate estimated from Australian cause-specific death rates. Event rates in each monthly cycle are transformed to transition probabilities.
Drug costs	Based on proposed effective PBS price for evolocumab
Acute event costs and health state costs	Based on PBS Statin Review (2012)
Utilities	Based on PBS Statin Review (2012)
Discount rate	5% for costs and outcomes
Software package	Excel 2010

Source: Table 3.1-1, p32 of the submission

Abbreviations: CTTC, Cholesterol Treatment Trialists' Collaborators; IS, ischaemic stroke; LDL, low density lipoprotein cholesterol; MI, myocardial infarction

6.28 The submission did not assess the cost-effectiveness of early treatment with evolocumab under the proposed listing versus delayed treatment with evolocumab

under the existing listing. The ESC considered a marginal cost-effectiveness analysis may have been informative, as the current submission represents a threshold expansion. Patients in the comparator arm close to qualifying under the current LDL-C criteria, but not adequately responding to optimised background treatment might present with higher LDL-C with repeated testing, and thus become eligible for evolocumab over time at the current 2.6 mmol/L LDL-C criteria. The model did not explicitly track LDL-C levels. The PSCR commented LDL-C would be very stable over time in an individual patient on maximum tolerated doses of statins and ezetimibe. However, the ESC noted that there were variations in LDL-C over time that would potentially affect eligibility for evolocumab.

- 6.29 Mean baseline LDL-C level (and corresponding cardiovascular risk) was the key driver of interest, as summarised in Table 11 below, given the economic model was otherwise essentially unchanged from that accepted in the November 2019 recommendation.

**Table 11: Key drivers of the model**

Description	Method/Value	Impact
Baseline LDL-C/ cardiovascular risk	<p>The mean baseline LDL-C in the expanded population with baseline LDL-C between 1.8 and 2.6 mmol/L was estimated from a new, sponsor-commissioned study of Australian GP consultations collected via the IQVIA database. The analysis of 778,107 total patients identified a subset of 331 patients with recorded diagnoses of MI, stroke, PAD, or 'other CHD', treated with ezetimibe with or without a concomitant statin, who had an LDL-C measurement between 1.8 and 2.6 mmol/L, recorded one to 6 months after receiving a script for lipid lowering therapy. The distribution of LDL-C levels among these patients was combined with assumed uptake rates (ranging from 5% for those with LDL-C 1.8 mmol/L to 60% for those with LDL-C 2.6 mmol/L) to generate a weighted average LDL-C of 2.325 mmol/L.</p> <p>The analysis was poorly documented and was of uncertain applicability to the Australian population, due to small numbers of patients, unspecified demographic details, and the unexplained exclusion of patients with diagnoses that would be eligible for treatment with evolocumab. Further, incorporation of poorly justified uptake assumptions to estimate a weighted mean LDL-C was inappropriate and resulted in a higher mean LDL-C (2.325 mmol/L) than for the unadjusted mean LDL-C in the sample (2.160 mmol/L). This resulted in a higher modelled baseline cardiovascular risk, a greater reduction in risk and therefore a greater treatment benefit for evolocumab compared to 'placebo'.</p>	Moderate, favours evolocumab

Source: Appendix 4 of the submission.

Abbreviations: CHD, coronary heart disease; GP, general practitioner; LDL, low density lipoprotein; MI, myocardial infarction; PAD, peripheral arterial disease

- 6.30 The average LDL-C for patients with an LDL-C > 2.6 mmol/L in the July 2019 submission was derived from individual patient data from the FOURIER trial. This trial had an LDL-C eligibility requirement of  $\geq 1.8$  mmol/L. No justification was provided in the current submission for the alternate approach taken to estimating average LDL-C in patients with LDL-C between 1.8 and 2.6 mmol/L (who would be the complement of the FOURIER subpopulation used to estimate mean LDL-C in the July and November 2019 submissions).
- 6.31 Results of the economic model are summarised in Table 12 below.

**Table 12: Results of the economic evaluation**

Component	Proposed medicine	Comparator	Increment
Costs	\$	\$	\$
QALYs	8.279	7.983	0.296
<b>Incremental cost/extra QALY gained</b>			\$

Source: Economic model\_Mar22.xlsx spreadsheet

Abbreviations: QALYs, quality-adjusted life years

The redacted values correspond to the following ranges:

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

- 6.32 Based on the economic model, treatment with evolocumab was associated with an incremental cost per QALY gained of \$25,000 to < \$35,000 compared to placebo (add-on to existing therapies) in non-familial hypercholesterolaemia patients with atherosclerotic disease and additional cardiovascular risk factors, and LDL-C levels between 1.8 and 2.6 mmol/L. This was the threshold ICER used to generate the proposed price of \$ per month.
- 6.33 The PSCR provided the mean LDL-C level at baseline in the FOURIER subgroup using the methodology from the previous submissions. For both reflexive and calculated LDL-C levels, the mean is 2.2 mmol/L. The PSCR maintained that it was appropriate to apply a higher baseline mean in the model to account for differential uptake. Using the mean from FOURIER increased the ICER to \$25,000 to < \$35,000 per QALY gained (shown in Table 15 below). The ESC considered there was potential face validity to an assumption that the mean LDL-C would be above the midpoint of 1.8 and 2.6 mmol/L (i.e., above 2.2 mmol/L), as there was potential for greater uptake in patients with higher LDL-C levels. However, the magnitude of the baseline level in the extended PBS population was highly uncertain, and therefore the ICER was also uncertain.
- 6.34 A comparison of the number of cardiovascular deaths, MIs, strokes and other major cardiovascular event avoided in the FOURIER trial compared to the economic model over a comparable time period, and at the 25-year time horizon was conducted during the evaluation (shown in Table 13).

**Table 13: Events per patient in the trial versus the economic model**

	FOURIER trial LDL-C > 1.8 mmol/L (median follow-up 2.2 years)			Economic model LDL-C > 1.8 ≤ 2.6 mmol/L (26 months, undiscounted)			Economic model LDL-C > 1.8 ≤ 2.6 mmol/L (25 years, undiscounted)		
	EVO	PBO	Incr.	EVO	PBO	Incr.	EVO	PBO	Incr.
Fatal CHD	1.8%	1.7%	0.10%	2.3%	2.3%	0	52.2%	58.8%	-6.6%
Life years	-	-	-	2.129	2.129	0	16.4	15.7	0.67
<b>Non-fatal CHD (events/patient)</b>									
MI ('heart attack')	0.0395	0.0540	-0.0145	0.0542	0.0722	-0.0180	0.7028	0.8289	-0.1261
Stroke	0.0159	0.0206	-0.0047	0.0207	0.0275	-0.0069	0.2682	0.3163	-0.0481

Source: compiled during the evaluation using analysis of individual patient data from FOURIER presented in the November 2019 PBAC PSD; and Economic model\_Mar 22 'Model' spreadsheet

Abbreviations: CHD, coronary heart disease; EVO, evolocumab; Incr., increment; MI, myocardial infarction; PBO, placebo

- 6.35 The risk of events (and the incremental benefit of evolocumab) was substantially higher over the 25-year timeframe for the economic model than in the trial because the model was based on a longer timeframe, with patients at increased risk of events

as they age over the model time horizon. At a more comparable time point in the model (26 months), the risk of fatal or non-fatal CHD events was still slightly higher in the model than in the FOURIER trial.

- 6.36 Table 14 compares the above-listed modelled outcomes for every 1,000 patients with LDL-C between 1.8 and 2.6 mmol/L treated with evolocumab compared with ‘placebo’ from the current submission, followed up for 25 years, to the same estimates for patients with LDL-C above 2.6 mmol/L presented in the November 2019 PBAC PSD (para 4.11, evolocumab PBAC PSD, November 2019 PBAC meeting).

**Table 14: Comparison of modelled outcomes for every 1,000 patients over a 25-year timeframe from November 2019 submission (patients with LDL > 2.6 mmol/L) and current economic model (LDL-C between 1.8 and 2.6 mmol/L)**

	Nov 2019 submission	Current submission
Evolocumab drug costs (including treatment discontinuations)	\$ [redacted] <sup>1</sup>	\$ [redacted] <sup>2</sup>
Fatal CHD events avoided	100	66
- resulting in life years gained per patient	1.1	0.67
Life years per CHD death avoided	11	10
Non-fatal MIs avoided	200	126
- resulting in treatment cost savings	\$ [redacted] <sup>3</sup>	\$ [redacted] <sup>3</sup>
Non-fatal strokes avoided	80	48
- resulting in treatment cost savings	\$ [redacted] <sup>3</sup>	\$ [redacted] <sup>3</sup>

Source: Calculated during the evaluation from ‘Economic model\_Mar 22’ Excel spreadsheet; para 4.11, evolocumab PBAC PSD, November 2019 PBAC meeting.

Abbreviations: CHD, coronary heart disease; MI, myocardial infarction

The redacted values correspond to the following ranges:

<sup>1</sup> \$20 million to < \$30 million

<sup>2</sup> \$10 million to < \$20 million

<sup>3</sup> \$0 to < \$10 million

- 6.37 Compared with the November 2019 model, the current model generates smaller incremental drug costs and disease management savings and fewer fatal and non-fatal CHD events avoided, consistent with the lower proposed price and lower risk population (LDL-C > 1.8 and ≤ 2.6 mmol/L compared to > 2.6 mmol/L).
- 6.38 The submission did not present sensitivity analyses for the economic model. During the evaluation, sensitivity analyses were conducted to assess the impact of varying the baseline mean LDL-C used in the model, using the upper and lower limit of the proposed LDL-C threshold (1.8 and 2.6 mmol/L), and the average LDL-C from the sponsor-commissioned analysis of the IQVIA GP database for patients, but without the application of the submission’s assumed uptake across LDL-C levels. The ICERs ranged from \$15,000 to < \$25,000 to \$55,000 to < \$75,000 per QALY gained. The ESC noted that the value proposition for this new lower risk patient population may be different to that previously accepted for the higher risk group. The ESC considered it may be informative for the PBAC to be presented with the drug cost resulting in ICERs of \$15,000 to < \$25,000 and \$15,000 to < \$25,000. These analyses are shown in Table 15 below, along with sensitivity analyses using 0% and 3.5% discount rates for costs and benefits, as requested in the PBAC Guidelines.

Table 15: Results of sensitivity analyses

	New population with LDL > 1.8 and ≤ 2.6 mmol/L					Overall population	
	Incremental cost	Incremental QALYs	ICER	Evolocumab price to achieve ICER <sup>a</sup>	Rebate on published DMPQ <sup>b</sup>	Weighted rebate <sup>c</sup>	Weighted average effective DPMQ
<b>Average LDL-C: 2.325 mmol/L</b>							
Base case: price based on \$25,000 to < \$35,000/QALY gained threshold	\$█	0.2957	\$█ <sup>1</sup>	\$█	█%	█%	140 mg: \$█ 420 mg: \$█
Price based on \$25,000 to < \$35,000/QALY threshold	\$█	0.2957	\$█ <sup>1</sup>	\$█	█%	█%	140 mg: \$█ 420 mg: \$█
Price based on \$15,000 to < \$25,000/QALY threshold	\$█	0.2957	\$█ <sup>2</sup>	\$█	█%	█%	140 mg: \$█ 420 mg: \$█
<b>Average LDL-C: 2.2 mmol/L (based on FOURIER, as reported in PSCR)</b>							
Price based on base case estimates	\$█	0.2675	\$█ <sup>1</sup>	\$█	█%	█%	140 mg: \$█ 420 mg: \$█
Price based on \$25,000 to < \$35,000/QALY threshold	\$█	0.2675	\$█ <sup>1</sup>	\$█	█%	█%	140 mg: \$█ 420 mg: \$█
Price based on \$25,000 to < \$35,000/QALY threshold	\$█	0.267	\$█ <sup>1</sup>	\$█	█%	█%	140 mg: \$█ 420 mg: \$█
Price based on \$15,000 to < \$25,000/QALY threshold	\$█	0.267	\$█ <sup>2</sup>	\$█	█%	█%	140 mg: \$█ 420 mg: \$█
<b>Discount rate adjustments (base case 5%)</b>							
3.5%; price based on base case estimates	\$█	0.3653	\$█ <sup>1</sup>	\$█	█%	█%	140 mg: \$█ 420 mg: \$█
0%; price based on base case estimates	\$█	0.6215	\$█ <sup>2</sup>	\$█	█%	█%	140 mg: \$█ 420 mg: \$█

Source: Calculated for the ESC advice using the Excel “goal seek” function with the Economic model\_Mar22.xlsx spreadsheet provided with the submission

Abbreviations: DPMQ, dispensed price for maximum quantity; ICER, incremental cost effectiveness ratio; LDL-C, low density lipoprotein cholesterol; QALY, quality adjusted life year

<sup>a</sup> Evolocumab price is the effective DPMQ for evolocumab 420 mg, with the effective DPMQ calculated for the 140 mg dose strength by adjusting for the 28 day supply (versus one month for the 420 mg dose strength) using the formula: 420 mg DPMQ x 12 / 365.25 x 28.

<sup>b</sup> The weighted rebate for the new population is calculated by using an 80%/20% split between the 140 mg and 420 mg dose strengths, respectively.

<sup>c</sup> Calculated using the proportions for new and existing populations as estimated in the submission (█████% patients with LDL-C between 1.8 and 2.6; █████% for patients with LDL-C > 2.6 mmol/L). The rebate on published DPMQ for the existing population is █████% as presented in the submission.

The redacted values correspond to the following ranges:

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

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

6.39 The price required to obtain an ICER of \$25,000 to < \$35,000 is sensitive to the average baseline LDL-C level of patients with LDL-C between 1.8 and 2.6 mmol/L and the discount rate.

### Drug cost/patient/year

6.40 The drug cost per patient for evolocumab in the new patient population is summarised in Table 16.

Table 16: Drug cost per patient for evolocumab

Treatment regimen	FOURIER trial		Economic analysis	Financial estimates	
	Evolocumab 140 mg fortnightly	Evolocumab 420 mg monthly	Evolocumab 140 mg fortnightly or 420 mg monthly	Evolocumab 140 mg fortnightly	Evolocumab 420 mg monthly
Compliance	-	-	-	85% <sup>b</sup>	
Persistence	88% <sup>a</sup>	-	99% <sup>c</sup>	-	
Adherence	Not reported		88% <sup>a</sup>	-	
Scripts/year	-	-	10.56 <sup>d</sup>	11.05 <sup>e</sup>	10.20 <sup>f</sup>
Cost/patient/script	-	-	\$█	\$█ <sup>g</sup>	\$█ <sup>g</sup>
Cost/patient/month	-	-	\$█ <sup>h</sup>	-	-
Fortnightly/monthly dosing split	Not reported		Not estimated	80% <sup>i</sup>	20% <sup>i</sup>
Cost/patient/year	-	-	\$█ <sup>j</sup>	\$█	

<sup>a</sup> Based on proportion of patients discontinuing treatment in the FOURIER trial

<sup>b</sup> Based on rate reported in review of statin therapies, as recommended by PBAC in November 2019 (para 4.30, evolocumab PSD, November 2019 PBAC meeting).

<sup>c</sup> Assumed 1% probability of stopping treatment each month in the first four years of treatment

<sup>d</sup> Based on assumed adherence rate (88%) and number of treatment cycles per year in the model (12)

<sup>e</sup> Based on assumed compliance rate (85%) and 13.04 scripts per patient per year

<sup>f</sup> Based on assumed compliance rate (85%) and 12 scripts per patient per year

<sup>g</sup> Effective DPMQ based on █████% rebate on government expenditure proposed in the submission for new population

<sup>h</sup> Effective DPMQ per script: \$█. Adjusted to monthly estimate \$█/30 (script duration in days) x 365.25/12 (days per month)

<sup>i</sup> Assumed

<sup>j</sup> Based on estimated scripts/year (10.56) and cost/patient/script (\$█)

<sup>k</sup> Based on scripts/year for fortnightly dose (11.05) and corresponding cost per script (\$█); scripts/year for monthly dose (10.20) and corresponding cost per script (\$█); weighted by assumed fortnightly/monthly dosing split (80% and 20% respectively)

### Estimated PBS usage & financial implications

6.41 This submission was considered by DUSC. The submission used an epidemiological approach to estimate the eligible patient population with FH and non-FH with ASCVD who have LDL-C levels between 1.8 and 2.6 mmol/L despite optimised treatment with statins and ezetimibe. The submission did not estimate the total financial impact of the new and existing patient population based on the submission's proposed weighted effective price. Key inputs are summarised in Table 17. The estimates in this section have not been updated to reflect the reduced price offered in the pre-PBAC response.

6.42 DUSC noted that the submission did not incorporate estimates of changed utilisation with the introduction of GP prescribing as proposed in the restriction. The sponsor had previously argued that there would be no additional financial impact beyond the existing financial estimates and RSA, as the financial estimates and patient numbers of the current RSA were calculated based on the assumption that GPs would be able to initiate treatment in consultation with a specialist physician (Para 2.3, evolocumab PSD, November 2020 PBAC meeting).

**Table 17: Key inputs for financial estimates**

Data	Value	Source	Comment
<b>Non-familial hypercholesterolaemia population estimates</b>			
Patients using ezetimibe with or without statins	362,810 (2018), 5% annual growth	Based on a DUSC secretariat analysis (Table 8, evolocumab PSD, November 2019 PBAC meeting) of a 10% Medicare sample of ezetimibe, and ezetimibe/statin combinations.	Assumption remains from previous submissions that all patients eligible for evolocumab must be currently treated with ezetimibe.
Ezetimibe patients with symptomatic ASCVD	69%	10% Medicare sample of ezetimibe utilisation (all formulations) in 2018 categorised by streamlined authority code.	Unchanged from July and November 2019 submissions.
Without underlying FH	96%	The submission stated that the population was assumed to be reduced by 4% (to avoid double counting of FH patients)	The source of this estimate was unclear.
At least one high risk factor	53%	Proportion of patients enrolled in FOURIER trial with at least one of the clinical eligibility factors from the current PBS restriction.	Rounded up from 52.8% estimated from FOURIER.
On ezetimibe for at least 3 months	80.1%	DUSC secretariat analysis (Table 8, evolocumab PSD, November 2019 PBAC meeting) of time on therapy for patients initiating ezetimibe ± statins from 2017 – 2019 using 10% Medicare sample.	-
Ezetimibe patients with LDL-C > 1.8 and ≤ 2.6 mmol/L	30%	Based on a sponsor-commissioned analysis of GP consultation records from IQVIA database: patients with prior record of MI, 'Other CHD', stroke or PAD treated with ezetimibe ± statin with most recent LDL-C measurement between 1.8 and 2.6 mmol/L	Methods of analysis and details of the included patient population were poorly documented in the submission. Based on subset of only 331 patients.

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Data	Value	Source	Comment
<b>Familial hypercholesterolaemia population estimates</b>			
FH prevalence	1:353 (0.283%)	Watts et al. (2015). Based on adult Australian patients with a phenotypic diagnosis of familial hypercholesterolaemia.	Unchanged from previous submissions
FH diagnosis rate	Yr 1: 70% Yrs 2-6: 75%	Assumption, based on published epidemiology estimates, accepted previously by PBAC (originally 35% in 2018, increasing to 75% in 2023).	It is unclear whether the assumptions of diagnosis originally estimated from 2018 to 2023, would continue to apply at a constant rate from 2023 onwards.
Proportion of FH patients with symptomatic ASCVD	40%	Assumption based on the proportion of adults aged ≥ 25 years with FH in the AusDiab cohort with symptomatic CV disease (51%) reported by Watts et al. (2015) and adjusted to apply to total Australian population.	Given the Australian population in the first step of the financial estimates was revised from total population to those aged 25 years or older, it is no longer appropriate to apply this adjusted proportion, and the 51% proportion should have been applied.
Percentage with LDL-C > 1.8 and ≤ 2.6 mmol/L	10%	The submission noted that 90% of patients in the RUTHERFORD-2 trial had a baseline LDL-C > 2.6 mmol/L, therefore the remaining 10% of patients were assumed to have LDL-C between 1.8 and 2.6 mmol/L.	The RUTHERFORD-2 trial only recruited patients with LDL-C above 2.6 mmol/L, and the minimum recorded LDL-C was 2.35 mmol/L.
<b>Utilisation estimates</b>			
Uptake rate	Yr 1: █████% Yr 2: █████% Yrs 3-6: █████%	Maximum uptake is a weighted average based on the distribution of 331 patients with LDL-C between 1.8 and 2.6 mmol/L (plus selected disease characteristics and record of recent ezetimibe ± statin use) from IQVIA GP dataset and assumed uptake (█████% for LDL-C 1.8 mmol/L, increasing to and █████% for LDL-C 2.6 mmol/L). Uptake in Years 1 and 2 assumed.	Uptake assumptions were highly uncertain and maximum uptake was derived from the distribution of a very small number of patients. In the November 2019 submission, uptake for patients with LDL-C between 2.6 and 3.3 mmol/L ranged from █████% to █████% for non-FH patients, and from █████% to █████% for FH patients.
Treatment compliance	85%	Based on rate reported in review of statin therapies, as recommended by PBAC in November 2019 (para 4.30, evolocumab PSD, November 2019 PBAC meeting).	This estimate was changed from 88% in the November 2019 submission, as trial-based estimates of treatment compliance were considered unlikely to be generalisable to clinical practice.

Source: Table 4.1-1, p35 of the submission; 'Financial Analysis\_Mar22' Excel spreadsheet; Table 4.5, evolocumab commentary, July 2019 PBAC meeting.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; DPMQ, dispensed price for maximum quantity; FH, familial hypercholesterolaemia; MI, myocardial infarction; PAD, peripheral arterial disease; PSD, public summary document.

6.43 The estimated uptake from non-FH patients with LDL-C in the proposed range between 1.8 and 2.6 mmol/L is summarised in Table 18 below.

**Table 18: Estimated utilisation and cost of evolocumab to the PBS/RPBS for patients with non-FH and ASCVD and additional risk factors, with LDL-C between 1.8 and 2.6 mmol/L despite optimised treatment with statins and ezetimibe**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Patients using ezetimibe ± statins	1	1	1	2	2	2
With symptomatic ASCVD (69%)	3	3	3	3	3	3
With non-FH (96%)	4	3	3	3	3	3
With ≥ 1 risk factor (53.0%)	5	5	5	5	5	5
On ezetimibe ≥ 3mths (80.1%)	5	5	5	5	5	5
<b>Eligible patients (with LDL-C &gt; 1.8 ≤ 2.6 mmol/L) (30%)</b>	6	6	7	7	7	7
Evolocumab uptake rate	%	%	%	%	%	%
<b>Total non-FH patients treated</b>	8	9	10	10	10	10
Patients - fortnightly dose (80%)	8	9	9	9	9	9
Evolocumab 140 mg scripts (11.05 scripts per patient)	6	11	12	12	5	5
Evolocumab 140 mg scripts (effective DPMQ \$ <sup>1</sup> )	\$13	\$13	\$14	\$14	\$14	\$14
Patients - monthly dose (20%)	8	8	8	8	8	8
Evolocumab 420 mg scripts (10.20 scripts per patient)	9	10	15	15	15	15
Evolocumab 420 mg scripts (effective DPMQ \$ <sup>1</sup> )	\$13	\$13	\$13	\$13	\$13	\$13
<b>Total cost (effective DPMQ)<sup>1</sup></b>	\$13	\$14	\$14	\$14	\$14	\$14
Patient copay (\$23.36/script)	-\$13	-\$13	-\$13	-\$13	-\$13	-\$13
<b>Total cost less copayment</b>	\$13	\$13	\$14	\$14	\$14	\$14

Source: Table 4.2-1, p36; Table 4.2-3, p37; Table 4.2-5, p38 of the submission; 'Financial Analysis\_Mar 22' Excel spreadsheet

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; DPMQ, dispensed price for maximum quantity; FH, familial hypercholesterolaemia; LDL, low-density lipoprotein.

<sup>1</sup> Effective prices used in the submission's calculations of financial impact were specific to the new population of patients with LDL-C 1.8 to 2.6 mmol/L

The redacted values correspond to the following ranges:

- <sup>1</sup> 400,000 to < 500,000
- <sup>2</sup> 500,000 to < 600,000
- <sup>3</sup> 300,000 to < 400,000
- <sup>4</sup> 200,000 to < 300,000
- <sup>5</sup> 100,000 to < 200,000
- <sup>6</sup> 30,000 to < 40,000
- <sup>7</sup> 40,000 to < 50,000
- <sup>8</sup> 500 to < 5,000
- <sup>9</sup> 5,000 to < 10,000
- <sup>10</sup> 10,000 to < 20,000
- <sup>11</sup> 60,000 to < 70,000
- <sup>12</sup> 90,000 to < 100,000
- <sup>13</sup> 0 to < \$10 million
- <sup>14</sup> \$10 million to < \$20 million
- <sup>15</sup> 20,000 to < 30,000

6.44 Based on effective prices specific to the new population, as offered in the submission, the net cost of extending the listing of evolocumab for the treatment of patients with non-familial hypercholesterolaemia with ASCVD and additional high risk factors and LDL-C between 1.8 and 2.6 mmol/L was estimated to be \$0 to < \$10 million in the first year of listing, increasing to \$10 million to < \$20 million in the sixth year of listing, a cumulative net cost over 6 years of \$70 million to < \$80 million.

- 6.45 The evaluation considered that the utilisation/financial estimates in the non-familial hypercholesterolaemia population were highly uncertain due to the following key issues:
- The proportion of non-FH patients with LDL-C between 1.8 and 2.6 mmol/L (30%) was based on a subgroup of patients from the sponsor commissioned IQVIA GP dataset analysis. This sample was small (331 patients), poorly documented, and of uncertain applicability to the overall Australian population.
  - Uptake estimates were highly uncertain and based on sponsor assumptions applied to the same small sample of data from the IQVIA database.
- 6.46 The DUSC considered that the treatment uptake rates were underestimated. DUSC noted that the chart audit conducted by the applicant that was used to inform the treatment uptake assumptions was done in acute patients and these patients were not necessarily representative of high-risk patients with a low-density lipoprotein cholesterol (LDL-C) level between 1.8 and 2.6 millimoles per litre.
- 6.47 Table 19 below compares the estimates of utilisation in the new population with those from the existing population in the November 2019 submission for patients with non-familial hypercholesterolaemia.

**Table 19: Utilisation estimates of evolocumab in the current submission (LDL-C 1.8 to 2.6 mmol/L) and November 2019 submission (LDL-C >2.6 mmol/L) for patients with non-FH and ASCVD with additional risk factors**

Non-FH patients only	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Current submission: LDL-C &gt;1.8 and ≤2.6 mmol/L</b>						
Eligible patients	1	1	2	2	2	2
Treated patients	3	4	5	5	5	5
Number of scripts	2	6	7	7	7	7
<b>Total cost less copayment</b>	<b>\$ 8</b>	<b>\$ 8</b>	<b>\$ 9</b>	<b>\$ 9</b>	<b>\$ 9</b>	<b>\$ 9</b>
<b>November 2019 submission: LDL-C &gt;2.6 mmol/L</b>						
Eligible patients <sup>1</sup>	1	2	2	10	10	11
Treated patients	4	5	12	1	1	1
Number of scripts	7	7	13	14	14	15
<b>Total cost less copayment</b>	<b>\$ 16</b>	<b>\$ 17</b>	<b>\$ 18</b>	<b>\$ 19</b>	<b>\$ 19</b>	<b>\$ 20</b>
<b>November 2019 DUSC re-analysis: LDL-C &gt;2.6 mmol/L</b>						
Eligible patients <sup>1</sup>	1	1	1	1	1	1
Treated patients	4	5	5	12	12	12
Number of scripts	6	7	7	13	13	13
<b>Total cost less copayment</b>	<b>\$ 9</b>	<b>\$ 16</b>	<b>\$ 17</b>	<b>\$ 21</b>	<b>\$ 18</b>	<b>\$ 18</b>

Source: Table 4.2-1, p36; Table 4.2-3, p37; Table 4.2-5, p38 of the submission; 'Financial Analysis\_Mar 22' Excel spreadsheet; 'Financial estimates\_additional use only with % rebate' Excel spreadsheet, November 2019 PBAC submission; DUSC re-analysis, November 2019 PBAC submission.

Abbreviations: LDL-C, low density lipoprotein cholesterol

<sup>1</sup> In the November 2019 submission, the eligible population was assumed to increase by 10% per year. This was modified to 5% annual growth in the DUSC-re-analysis of utilisation.

The redacted values correspond to the following ranges:

- <sup>1</sup> 30,000 to < 40,000
- <sup>2</sup> 40,000 to < 50,000
- <sup>3</sup> 500 to < 5,000
- <sup>4</sup> 5,000 to < 10,000
- <sup>5</sup> 10,000 to < 20,000
- <sup>6</sup> 80,000 to < 90,000
- <sup>7</sup> 100,000 to < 200,000
- <sup>8</sup> \$0 to < \$10 million
- <sup>9</sup> \$10 million to < \$20 million
- <sup>10</sup> 50,000 to < 60,000
- <sup>11</sup> 60,000 to < 70,000
- <sup>12</sup> 20,000 to < 30,000
- <sup>13</sup> 200,000 to < 300,000
- <sup>14</sup> 300,000 to < 400,000
- <sup>15</sup> 400,000 to < 500,000
- <sup>16</sup> \$20 million to < \$30 million
- <sup>17</sup> \$30 million to < \$40 million
- <sup>18</sup> \$50 million to < \$60 million
- <sup>19</sup> \$70 million to < \$80 million
- <sup>20</sup> \$80 million to < \$90 million
- <sup>21</sup> \$40 million to < \$50 million

6.48 Compared to the DUSC re-analysis of the November 2019 submission utilisation estimates for evolocumab in patients with non-FH and LDL-C > 2.6 mmol/L, which used similar assumptions, the current submission estimated a slightly higher number of patients that would be eligible for treatment in the lower LDL-C range, but a lower number of patients opting for treatment with evolocumab. This is in contrast to the submission's IQVIA database sample, that suggested the number of eligible patients with LDL-C between 1.8 and 2.6 mmol/L was almost double that of the patients with LDL-C above 2.6 mmol/L. The DUSC noted these inconsistencies created doubt about

the generalisability of the audit results to the Australian population. The evaluation considered that despite the potential for lower uptake in patients with lower LDL-C, the likely much larger size of the eligible population means that utilisation in the non-FH patients may have been underestimated.

- 6.49 The estimated uptake from heterozygous FH patients with LDL-C in the proposed range between 1.8 and 2.6 mmol/L is summarised in Table 20 below. The submission noted that, as in the previous November 2019 evolocumab submission, the homozygous FH population was not considered in these estimates. While the reduction in LDL-C threshold was proposed to apply to the homozygous FH listing to ensure consistency across listings, it was not anticipated to result in any additional eligible patients. The PBAC previously accepted the exclusion of the homozygous FH population from utilisation estimates for lower LDL-C ranges, considering that these patients were highly unlikely to have LDL-C within the 2.6-3.3 mmol/L range (evolocumab PSD, November 2019 PBAC meeting). Patients with homozygous FH are even less likely to have LDL-C within the 1.8-2.6 mmol/L range.

**Table 20: Estimated utilisation and cost of evolocumab to the PBS/RPBS for patients with heterozygous FH and ASCVD with LDL-C between 1.8 and 2.6 mmol/L despite optimised treatment with statins and ezetimibe**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Australian population ≥25 yrs	18,325,590	18,633,517	18,937,442	19,236,668	19,529,609	19,809,954
Prevalence of FH (1:353)	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
FH diagnosis rate	█ <sup>2</sup> %	█ <sup>2</sup> %	█ <sup>2</sup> %	█ <sup>2</sup> %	█ <sup>2</sup> %	█ <sup>2</sup> %
Diagnosed FH patients	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
W/ symptomatic ASCVD (40%)	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
<b>Additional eligible patients LDL-C &gt; 1.8 ≤ 2.6 mmol/L (10%)</b>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>
Evolocumab uptake rate	█ <sup>6</sup> %	█ <sup>6</sup> %	█ <sup>6</sup> %	█ <sup>6</sup> %	█ <sup>6</sup> %	█ <sup>6</sup> %
<b>Total FH patients</b>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>
Patients - fortnightly dose (80%)	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>
Evolocumab 140 mg scripts (11.05 scripts per patient)	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>
Effective cost of evolocumab 140 mg scripts (\$█ <sup>7</sup> ) <sup>1</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>
Patients - monthly dose (20%)	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>
Evolocumab 420 mg scripts (10.20 scripts per patient)	█ <sup>6</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>
Effective cost of evolocumab 420 mg scripts (\$█ <sup>7</sup> ) <sup>1</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>
<b>Total cost (effective DPMQ)<sup>1</sup></b>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>
Patient co-pay (\$23.36/script)	-\$█ <sup>7</sup>	-\$█ <sup>7</sup>	-\$█ <sup>7</sup>	-\$█ <sup>7</sup>	-\$█ <sup>7</sup>	-\$█ <sup>7</sup>
<b>Total cost less co-payment</b>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>

Source: Table 4.2-2, p37; Table 4.2-3, p37; Table 4.2-5, p38 of the submission; 'Financial Analysis\_Mar 22' Excel spreadsheet

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; DPMQ, dispensed price for maximum quantity; FH, familial hypercholesterolaemia; LDL, low-density lipoprotein.

<sup>1</sup> Effective prices used in the submission's calculations of financial impact were specific to the new population of patients with LDL-C 1.8 to 2.6 mmol/L

The redacted values correspond to the following ranges:

<sup>1</sup> 50,000 to < 60,000

<sup>2</sup> 30,000 to < 40,000

<sup>3</sup> 40,000 to < 50,000

<sup>4</sup> 10,000 to < 20,000

<sup>5</sup> 500 to < 5,000

<sup>6</sup> < 500

<sup>7</sup> \$0 to < \$10 million

- 6.50 Based on effective prices specific to the new population, the net cost of extending the listing of evolocumab for the treatment of patients with familial hypercholesterolaemia with ASCVD and LDL-C between 1.8 and 2.6 mmol/L was estimated to be \$0 to < \$10 million in the first year of listing, increasing to \$0 to < \$10 million in the sixth year of listing, a cumulative net cost over 6 years of \$0 to < \$10 million.
- 6.51 The evaluation considered that the utilisation/financial estimates in the familial hypercholesterolaemia population were uncertain due to the following issues:
- The proportion of FH patients with ASCVD used in previous submissions (and derived from the AusDiab cohort of patients aged 25 years and older) was adjusted to account for the inclusion of the total Australian population in the first step of the estimated utilisation rather than those aged over 25 as recommended by DUSC (Table 8, evolocumab PSD, November 2019 PBAC meeting). In the current submission the Australian population aged 25 years and older was appropriately used, but the adjusted proportion of FH patients with ASCVD (40%) rather than the original estimate of 51% was still applied, meaning that the number of eligible patients was underestimated.
  - In the July 2019 submission, it was assumed that 90% of patients from the RUTHERFORD-2 trial of familial hypercholesterolaemia patients had LDL-C > 2.6 mmol/L. The current submission stated that all participants in this trial had LDL-C above 1.8 mmol/L, therefore the remaining 10% of patients in this sample were assumed to have LDL-C between 1.8 and 2.6 mmol/L. The RUTHERFORD-2 trial was not a reliable data source as the minimum LDL-C to be eligible for the trial was 2.6 mmol/L.
  - Uptake estimates were highly uncertain and based on sponsor assumptions applied to a small sample of data from the IQVIA database.
- 6.52 Table 21 below compares the estimates of utilisation in the new population with those from the existing population with LDL-C between 2.6 and 3.3 mmol/L in the November 2019 submission for patients with HeFH.

**Table 21: Estimates of eligible patients and utilisation of evolocumab in current submission (LDL-C > 1.8 and ≤ 2.6 mmol/L) and November 2019 submission (LDL-C > 2.6 and ≤ 3.3 mmol/L) for patients with heterozygous FH and ASCVD**

HeFH patients only	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Current submission: LDL-C &gt; 1.8 and ≤ 2.6 mmol/L</b>						
Eligible patients	1	1	1	1	1	1
Treated patients	2	2	2	2	2	2
Number of scripts	1	1	1	1	1	1
<b>Total cost less co-payment</b>	<b>\$ 3</b>	<b>\$ 3</b>	<b>\$ 3</b>	<b>\$ 3</b>	<b>\$ 3</b>	<b>\$ 3</b>
<b>November 2019 submission: LDL-C &gt; 2.6 and ≤ 3.3 mmol/L</b>						
Eligible patients	4	4	5	5	5	5
Treated patients	1	4	4	4	4	4
Number of scripts	6	7	8	9	9	9
<b>Total cost less co-payment</b>	<b>\$ 3</b>	<b>\$ 10</b>	<b>\$ 10</b>	<b>\$ 10</b>	<b>\$ 10</b>	<b>\$ 10</b>
<b>November 2019 DUSC re-analysis: LDL-C &gt; 2.6 and ≤ 3.3 mmol/L</b>						
Eligible patients	4	4	4	4	4	4
Treated patients	1	1	1	4	4	4
Number of scripts	11	12	6	7	7	7
<b>Total cost less copayment</b>	<b>\$ 3</b>	<b>\$ 3</b>	<b>\$ 3</b>	<b>\$ 10</b>	<b>\$ 10</b>	<b>\$ 10</b>

Source: Table 4.2-2, p37; Table 4.2-3, p37; Table 4.2-5, p38 of the submission; 'Financial Analysis\_Mar 22' Excel spreadsheet; 'Financial estimates\_additional use only with % rebate' Excel spreadsheet, November 2019 PBAC submission; DUSC re-analysis, November 2019 PBAC submission.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; DPMQ, dispensed price for maximum quantity; FH, familial hypercholesterolaemia; LDL, low-density lipoprotein.

The redacted values correspond to the following ranges:

<sup>1</sup> 500 < 5,000

<sup>2</sup> < 500

<sup>3</sup> \$0 to < \$10 million

<sup>4</sup> 5,000 to < 10,000

<sup>5</sup> 10,000 to < 20,000

<sup>6</sup> 40,000 to < 50,000

<sup>7</sup> 60,000 to < 70,000

<sup>8</sup> 80,000 to < 90,000

<sup>9</sup> 90,000 to < 100,000

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

<sup>11</sup> 20,000 to < 30,000

<sup>12</sup> 30,000 to < 40,000

6.53 The number of eligible and treated familial hypercholesterolaemia patients with LDL-C between 1.8 and 2.6 mmol/L estimated in the current submission was considerably smaller than the number of patients with LDL-C between 2.6 and 3.3 mmol/L estimated in the November 2019 submission.

6.54 The total financial implications across all patient populations using the base case effective price specific to the new population are summarised in

6.55 Table 22.

**Table 22: Estimated budget impact of extending the PBS/RPBS listing of evolocumab for patients with LDL-C 1.8 to 2.6 mmol/L**

	Year 1 (2022)	Year 2 (2023)	Year 3 (2024)	Year 4 (2025)	Year 5 (2026)	Year 6 (2027)
Total scripts	[redacted] <sup>1</sup>	[redacted] <sup>2</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>
Expanded non-FH listing	\$ [redacted] <sup>4</sup>	\$ [redacted] <sup>4</sup>	\$ [redacted] <sup>5</sup>	\$ [redacted] <sup>5</sup>	\$ [redacted] <sup>5</sup>	\$ [redacted] <sup>5</sup>
Expanded FH listing	\$ [redacted] <sup>4</sup>	\$ [redacted] <sup>4</sup>	\$ [redacted] <sup>4</sup>	\$ [redacted] <sup>4</sup>	\$ [redacted] <sup>4</sup>	\$ [redacted] <sup>4</sup>
<b>Total cost to PBS/RPBS</b>	<b>\$ [redacted]<sup>4</sup></b>	<b>\$ [redacted]<sup>5</sup></b>	<b>\$ [redacted]<sup>5</sup></b>	<b>\$ [redacted]<sup>5</sup></b>	<b>\$ [redacted]<sup>5</sup></b>	<b>\$ [redacted]<sup>5</sup></b>

Source: Table 4.2-7, p39 of the submission

Abbreviations: FH, familial hypercholesterolaemia

Note: Effective prices used in the submission's calculations of financial impact were specific to the new population of patients with LDL-C 1.8 to 2.6 mmol/L

The redacted values correspond to the following ranges:

<sup>1</sup> 40,000 to < 50,000

<sup>2</sup> 80,000 to < 90,000

<sup>3</sup> 100,000 to < 200,000

<sup>4</sup> \$0 to < \$10 million

<sup>5</sup> \$10 million to < \$20 million

6.56 The estimated cumulative net cost across the new population was \$70 million to < \$80 million over 6 years.

### Quality Use of Medicines

6.57 Quality use of medicines issues were not addressed in the submission. The DUSC noted that evolocumab is no longer a novel agent. However, training programs should be implemented to further familiarise GPs with evolocumab.

### Financial Management – Risk Sharing Arrangements

6.58 The submission noted there is an established two-tier subsidisation cap arrangement based on forecast utilisation for the PCSK9 inhibitor class for current PBS listings. Any expenditure between Tier 1 and 2 caps attracts an additional 10% rebate and any expenditure over Tier 2 caps would be rebated in full. The submission stated that the sponsor is willing to agree to a revised arrangement for evolocumab that mirrors the existing arrangement with an increase in caps reflective of the increase in patient numbers and cost to the PBS/RPBS represented by the proposed expanded listing.

6.59 The sponsor had previously stated that the financial estimates and patient numbers of the current RSA were calculated based on the assumption that GPs would be able to initiate treatment in consultation with a specialist physician (para 2.3, evolocumab PSD, November 2020 PBAC meeting).

## **7 PBAC Outcome**

- 7.1 The PBAC recommended extending the existing PBS listings for evolocumab for hypercholesterolaemia, to include patients who have an LDL-C level between 1.8 and 2.6 mmol/L despite optimised treatment with statins and ezetimibe, and to allow initial prescribing by any medical practitioner in consultation with a specialist physician.
- 7.2 The PBAC is satisfied that evolocumab provides, for some patients, a significant improvement in efficacy over optimised background treatment, in the extended population.
- 7.3 The PBAC advised that the expanded LDL-C criteria were consistent with current international clinical guidelines and the expanded prescriber criteria would reduce current equity and access issues associated with initiation only by specialists. The PBAC also advised that the listing would be cost-effective at a reduced price resulting in an incremental cost-effectiveness ratio (ICER) of \$25,000 to < \$35,000 per QALY gained, but that no increases to the current expenditure caps under the existing Risk Sharing Arrangement (RSA) were justified.
- 7.4 The PBAC noted that the consumer comments were supportive of the expanded listing, and that they highlighted how initiation only by specialists raised equity issues, in particular for patients outside major urban centres, for patients with lower socio-economic status or poor mental health, as well as for older Australians and Aboriginal and/or Torres Strait Islander populations.
- 7.5 The PBAC considered that the clinical positioning of evolocumab was appropriate – as a treatment option in patients with LDL-C levels above 1.8 mmol/L despite optimised treatment with statins and ezetimibe (or despite optimised treatment with statins for HoFH patients). It noted that the threshold was generally consistent with current international clinical guidelines, as well as previous guidelines, but that the original listing had been targeted to a more restricted population in whom the treatment was expected to be most cost-effective.
- 7.6 The PBAC remained of the view that optimised background treatment was the appropriate comparator in the expanded population.
- 7.7 The PBAC noted that it had previously reviewed the key clinical evidence to support the listing – the FOURIER trial, a randomised double-blind head-to-head comparison of cardiovascular outcomes with evolocumab versus placebo in hypercholesterolaemia patients with atherosclerotic cardiovascular disease. The PBAC recalled that majority of patients in the FOURIER trial had baseline LDL-C levels between 1.8 and 2.6 mmol/L, with an average of 2.532 and 2.529 mmol/L in the evolocumab and placebo arms respectively.
- 7.8 The PBAC recalled that treatment with evolocumab was associated with a statistically significant decreased risk of cardiovascular events compared to ‘placebo’ and noted that benefits of evolocumab were largely consistent across major subgroups.

- 7.9 Based on the FOURIER trial, the PBAC considered that evolocumab plus optimised background treatment has superior effectiveness compared with optimised background treatment for the expanded population. The PBAC agreed with the ESC's assessment that the same proportional benefit was expected to be achieved across different LDL-C percentile ranges, with lower absolute treatment benefit expected due to lower baseline risk in the proposed additional patient group. The PBAC considered that the safety would be similar compared to optimised background treatment.
- 7.10 The PBAC noted that the submission presented a cost-utility analysis of evolocumab for the treatment of non-familial hypercholesterolaemia patients with atherosclerotic disease and additional risk factors, who have an LDL-C level between 1.8 and 2.6 mmol/L despite optimised treatment with statins and ezetimibe. The PBAC noted that the model was broadly similar to that it had previously considered (see paragraphs 6.25 and 6.26), and whilst it agreed with the ESC that a marginal analysis would have been technically preferable (paragraph 6.28), it accepted the submitted model structure had been relied on previously and was adequate for decision making. However, the modelled average baseline LDL-C level (2.325 mmol/L) was derived using a sponsor-commissioned study of GP records combined with somewhat arbitrary uptake assumptions, which was a less reliable methodology than using individual patient data from the FOURIER trial (resulting in baseline mean of 2.2 mmol/L), which had been the approach in previous submissions, and which was calculated for the PSCR. Furthermore, the PBAC noted that the submissions' base case ICER of \$25,000 to < \$35,000 per QALY gained increased to \$25,000 to < \$35,000 per QALY gained when a mean baseline LDL-C of 2.2 mmol/L was used.
- 7.11 The PBAC recalled that, in the context of a secondary prevention treatment with an unknown magnitude of mortality benefit, it had previously considered that an ICER of less than \$25,000 to < \$35,000 per QALY gained would be required for cost-effectiveness for the listing for non-familial hypercholesterolaemia patients in November 2019. The PBAC considered that the value proposition in this new lower risk patient population was reasonably at a lower threshold, and thus considered that the expanded listings would be cost-effective at an ICER of less than \$25,000 to < \$35,000 per QALY gained (and using a mean baseline LDL-C of 2.2 mmol/L). As with its November 2019 consideration, the PBAC considered that the cost-effectiveness could be inferred for an expanded FH listing, based on the non-FH model, at the same price as accepted for non-FH (para 3.4, evolocumab PSD, November 2019 PBAC meeting).
- 7.12 The PBAC noted that the submission had proposed a weighted price across the existing PBS listings and the expanded population (1%:1%), based on the existing RSA caps combined with the submission's forecast for the new services. The PBAC noted that these estimates were based on the estimated size of the eligible population and the assumed uptake, both of which were highly uncertain. The pre-PBAC proposed a revised reduced overall weighted price, which it stated reflected an increase in the

weighting of the additional population from  $\frac{1}{2}\%$  to  $\frac{1}{4}\%$ . The PBAC noted that there was no justification for this estimate, but considered that a more conservative weighting was appropriate in view of the considerable uncertainty.

- 7.13 The PBAC noted that expenditure under the current RSA was tracking substantially below the caps, and considered that even with the expanded listing, the utilisation was likely to remain within these caps. Therefore, increasing the caps would not provide an effective mechanism for managing uncertainties associated with the expanded listing.
- 7.14 The PBAC noted the DUSC's advice that the treatment uptake rates were underestimated, that the eligible population estimates were inconsistent with previous submissions and that the proposed restriction change to allow GP prescribing was not accounted for. However, the PBAC also noted that the sponsor had previously argued there would be no additional financial impact due to GP prescribing as it claimed that previous estimates were calculated based on the assumption that GPs would be able to initiate treatment in consultation with a specialist physician. The PBAC considered it was unlikely that more reliable sources were available for the estimates in the new population, and while inconsistencies contributed further uncertainty, the submission's estimates reflected a reasonable basis for costing the financial impact to the Australian Government, with the exception that the proportion of FH patients with ASCVD should be revised from 40% to 51% to reflect those aged 25 years and over, as this was consistent with the estimation of the Australian population in the first step of the financial estimates.
- 7.15 With respect to the request for GP initial prescribing, the PBAC recalled its previous concerns when the same request was considered in November 2020 that given the recency of the listing at the time, it would be appropriate to wait for a DUSC review of utilisation at least 18 months from the date that the non-FH listing was added (see Table 2). The PBAC noted that 27 months had passed since the non-FH listing was added and that the DUSC review was not due until February 2023 at the earliest. The PBAC considered that there remained a risk of use outside the restriction, but that retaining an Authority Required (Telephone/Electronic) listing would help to mitigate this, and furthermore, the current expenditure provided reassurance that there was limited financial risk to the Australian Government from the expanded listing.
- 7.16 In terms of the restriction, the PBAC noted that the sole changes related to the prescriber type on the initial phase listings and the LDL-C threshold, which were appropriate for the non-FH, HoFH and HeFH listings. The PBAC considered that the request for grandfathering for non-FH and HeFH was reasonable but noted that the grandfathering request was not made for the HoFH population. Given the small size and likely overall higher LDL-C levels in this population, the PBAC considered it unlikely that grandfathering would be required in this group. The PBAC advised that the grandfathering listings should be in operation for 12 months, with a relevant administrative note added.

- 7.17 The PBAC recalled that it had previously considered the ODYSSEY OUTCOMES trial (alirocumab versus placebo), which had a qualifying LDL-C threshold of  $\geq 1.8$  mmol/L and it recalled that the alirocumab listing thresholds were defined based on prior PBAC decisions in regard to evolocumab (paragraph 2.12, alirocumab PSD, March 2019 PBAC Meeting). The PBAC considered that the recommendations with regard to evolocumab should flow on to alirocumab at the established pricing relativities as there would be no requirement for further assessment of the clinical and cost-effectiveness of alirocumab.
- 7.18 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 evolocumab:
- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy, over alternative therapies, on the basis of approximately 60% reduction in LDL-C levels over the FOURIER trial duration and decreased risk of myocardial infarction, coronary revascularisation and ischaemic stroke compared to placebo;
  - b) The treatment is not expected to address a high and urgent unmet clinical need due to the existence of other therapies for this condition being available on the PBS;
  - 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.
- 7.19 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

### 8.1 Amend existing listings as follows:

**11484K, 11485L Restriction Summary 11990 / ToC: 12008: Authority Required**

[25722]	<b>Clinical criteria:</b>
[25723]	Patient must have an LDL cholesterol level in excess of <del>2.6</del> 1.8 millimoles per litre in the presence of symptomatic atherosclerotic cardiovascular disease; or

**11484K, 11485L Restriction Summary 11991 / ToC: 12012: Authority Required**

[25661]	<b>Clinical criteria:</b>
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[25660]	Patient must have an LDL cholesterol level in excess of <del>2.6</del> 1.8 millimoles per litre
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10958R, 11193D Restriction Summary 12030 / ToC: 10380: Authority Required

[25661]	<b>Clinical criteria:</b>
[25660]	Patient must have an LDL cholesterol level in excess of <del>2.6</del> 1.8 millimoles per litre

On all of the above prescribing rules:

[22846]	<b>Treatment criteria:</b>
[22845]	Must be treated by <i>or in consultation with</i> a specialist physician

8.2 Add grandfathering phase listings to evolocumab as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
EVOLOCUMAB					
evolocumab 140 mg/mL injection, 1 mL pen device	11484K	2	2	5	Repatha
evolocumab 420 mg/3.5 mL injection, 3.5 mL cartridge	11485L	1	1	5	Repatha
<b>Restriction Summary [new] / Treatment of Concept: [new]</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 (telephone/online PBS Authorities system)					
<b>Indication:</b> Non-familial hypercholesterolaemia					
<b>Treatment Phase:</b> Grandfather treatment					
<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>Administrative Advice:</b> Special Pricing Arrangements apply.					
<b>Clinical criteria:</b>					
Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [insert listing date]					
<b>AND</b>					
<b>Clinical criteria:</b>					
The treatment must be in conjunction with dietary therapy and exercise,					
<b>AND</b>					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must have had symptomatic atherosclerotic cardiovascular disease prior to starting non-PBS-subsidised treatment with this drug for this condition,					

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	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have had an LDL cholesterol level in excess of 1.8 millimoles per litre prior to starting non-PBS-subsidised treatment with this drug for this condition,
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have had atherosclerotic disease in two or more vascular territories (coronary, cerebrovascular or peripheral vascular territories) prior to starting non-PBS-subsidised treatment with this drug for this condition; or
	Patient must have had severe multi-vessel coronary heart disease defined as at least 50% stenosis in at least two large vessels prior to starting non-PBS-subsidised treatment with this drug for this condition; 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 prior to starting non-PBS-subsidised treatment with this drug for this condition; or
	Patient must have had diabetes mellitus with microalbuminuria prior to starting non-PBS-subsidised treatment with this drug for this condition; or
	Patient must have had diabetes mellitus and be aged 60 years of more prior to starting non-PBS-subsidised treatment with this drug for this condition; or
	Patient must be an Aboriginal or Torres Strait Islander with diabetes mellitus that was present prior to starting non-PBS-subsidised treatment with this drug for this condition; or
	Patient must have had a Thrombolysis in Myocardial Infarction (TIMI) Risk Score for Secondary Prevention of 4 or higher prior to starting non-PBS-subsidised treatment with this drug for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have been treated with the maximum recommended dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily) 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 prior to initiating non-PBS-subsidised treatment with this drug for this condition; or
	Patient must have developed a clinically important product-related adverse event necessitating withdrawal of statin treatment to trials of each of atorvastatin and rosuvastatin prior to initiating non-PBS-subsidised treatment with this drug for this condition; 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 been treated with ezetimibe for at least 12 consecutive weeks in conjunction with a statin (if tolerated), dietary therapy and exercise prior to initiating non-PBS-subsidised treatment with this drug for this condition
	<b>AND</b>
	<b>Treatment criteria:</b>
	Must be treated by or in consultation with a specialist physician
	<b>Prescribing Instructions:</b> 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

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	<p>(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</p> <p>(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)).</p>
	<p><b>Prescribing Instructions:</b></p> <p>The qualifying LDL cholesterol level must have been measured 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 have been no more than 8 weeks old at the time non-PBS-subsidised treatment with this drug for this condition was initiated.</p>
	<p><b>Prescribing Instructions:</b></p> <p>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></p> <p>If treatment with atorvastatin or rosuvastatin resulted in development of a clinically important product-related adverse event resulting in treatment withdrawal, the patient must have been treated with the alternative statin (atorvastatin or rosuvastatin) unless there was a contraindication (e.g. prior rhabdomyolysis) to the alternative statin. This retrial should have occurred after a washout period of at least 4 weeks, or if the creatine kinase (CK) level was elevated, the retrial should not have occurred until CK had returned to normal.</p>
	<p><b>Prescribing Instructions:</b></p> <p>In the event of a trial of the alternative statin, the dose of the alternative statin should have been increased not more often than every 4 weeks until the maximum tolerated dose was reached or target LDL-c had been achieved.</p>
	<p><b>Prescribing Instructions:</b></p> <p>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> <p>(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</p> <p>(ii) the doses, duration of treatment and details of adverse events experienced with trials with each of atorvastatin and rosuvastatin; or</p> <p>(iii) the patient is contraindicated to treatment with a statin as defined in the TGA-approved Product Information.</p>
	<p><b>Prescribing Instructions:</b></p> <p>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:</p> <p>(i) atherosclerotic disease in two or more vascular territories (coronary, cerebrovascular or peripheral vascular territories); or</p> <p>(ii) severe multi-vessel coronary heart disease defined as at least 50% stenosis in at least two large vessels; or</p> <p>(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</p> <p>(iv) diabetes mellitus with microalbuminuria; or</p>

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	(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
	<b>Prescribing Instructions:</b> A patient may qualify for PBS-subsidised treatment under this restriction once only.
	<b>Prescribing Instructions:</b> For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
	<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.
<b>Restriction Summary [new] / Treatment of Concept: [new]</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 (telephone/online PBS Authorities system)
	<b>Indication:</b> Familial heterozygous hypercholesterolaemia
	<b>Treatment Phase:</b> Grandfather treatment
	<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>Administrative Advice:</b> Special Pricing Arrangements apply.
	<b>Clinical criteria:</b>
	Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [insert listing date]
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be in conjunction with dietary therapy and exercise,
	<b>AND</b>
	<b>Clinical criteria:</b>
	The condition must have been confirmed by genetic testing prior to starting non-PBS-subsidised treatment with this drug for this condition; or
	The condition must have been confirmed by a Dutch Lipid Clinic Network Score of at least 6 prior to starting non-PBS-subsidised treatment with this drug for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have had an LDL cholesterol level in excess of 1.8 millimoles per litre in the presence of symptomatic atherosclerotic cardiovascular disease at the time non-PBS-subsidised treatment with this drug for this condition was initiated
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have been treated with the maximum recommended dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily) 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 prior to initiating non-PBS-subsidised treatment with this drug for this condition; or

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	Patient must have developed a clinically important product-related adverse event necessitating withdrawal of statin treatment to trials of each of atorvastatin and rosuvastatin prior to initiating non-PBS-subsidised treatment with this drug for this condition; 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 been treated with ezetimibe for at least 12 consecutive weeks in conjunction with a statin (if tolerated), dietary therapy and exercise prior to initiating non-PBS-subsidised treatment with this drug for this condition
	<b>AND</b>
	<b>Treatment criteria:</b>
	Must be treated by or in consultation with a specialist physician
	<b>Prescribing Instructions:</b> 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)).
	<b>Prescribing Instructions:</b> The qualifying LDL cholesterol level must have been measured 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 have been no more than 8 weeks old at the time non-PBS-subsidised treatment with this drug for this condition was initiated.
	<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> If treatment with atorvastatin or rosuvastatin resulted in development of a clinically important product-related adverse event resulting in treatment withdrawal, the patient must have been treated with the alternative statin (atorvastatin or rosuvastatin) unless there was a contraindication (e.g. prior rhabdomyolysis) to the alternative statin. This retrial should have occurred after a washout period of at least 4 weeks, or if the creatine kinase (CK) level was elevated, the retrial should not have occurred until CK had returned to normal.
	<b>Prescribing Instructions:</b> In the event of a trial of the alternative statin, the dose of the alternative statin should have been increased not more often than every 4 weeks until the maximum tolerated dose was reached or target LDL-c had been achieved.

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	<p><b>Prescribing Instructions:</b> The following must be stated at the time of application and documented in the patient's medical records: (i) the qualifying Dutch Lipid Clinic Network Score; or (ii) the result of genetic testing confirming a diagnosis of familial heterozygous hypercholesterolaemia</p>
	<p><b>Prescribing Instructions:</b> 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.</p>
	<p><b>Prescribing Instructions:</b> A patient may qualify for PBS-subsidised treatment under this restriction once only.</p>
	<p><b>Prescribing Instructions:</b> For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.</p>
	<p><b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a>) or by telephone by contacting Services Australia on 1800 888 333.</p>

8.3 Amend existing alirocumab listings as follows:

12604J, 12613W *Restriction Summary 11990 / ToC: 12008: Authority Required*

	<p><b>Clinical criteria:</b></p>
	<p>Patient must have an LDL cholesterol level in excess of <del>2.6</del> 1.8 millimoles per litre in the presence of symptomatic atherosclerotic cardiovascular disease; or</p>

12604J, 12613W *Restriction Summary 12053 / ToC: 12054: Authority Required*

	<p><b>Clinical criteria:</b></p>
	<p>Patient must have an LDL cholesterol level in excess of <del>2.6</del> 1.8 millimoles per litre prior to commencing treatment with a monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9),</p>

On all of the above prescribing rules:

	<p><b>Treatment criteria:</b></p>
	<p>Must be treated by <i>or in consultation with</i> a specialist physician</p>

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

## **9 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.

## **10 Sponsor's Comment**

Amgen is pleased that evolocumab will soon be available on the PBS for more Australian patients with hypercholesterolaemia at high risk of cardiovascular events.