

7.07 EVOLOCUMAB,

**Injection 420 mg in 3.5 mL single use pre-filled cartridge,
Injection 140 mg in 1 mL single use pre-filled pen,
Repatha[®],
Amgen Australia Pty Ltd**

1 Purpose of Application

- 1.1 The resubmission requested a Section 85 (Authority Required) PBS listing for evolocumab for the treatment of non-familial hypercholesterolaemia in patients with atherosclerotic cardiovascular disease (ASCVD) who have additional risk factors. The resubmission also requested an extension of the current Section 85 (Authority Required) PBS listing of evolocumab for the treatment of familial hypercholesterolaemia (FH) to include patients with ASCVD who have an LDL level between 2.6 and 3.3 mmol/L despite optimised treatment with statins and ezetimibe.
- 1.2 The PBAC has previously considered six submissions for evolocumab at the March 2015, March 2016, July 2017 (minor submission), November 2017, March 2018 (minor submission) and July 2018 meetings.
- 1.3 Listing was requested on a cost-effectiveness basis compared to placebo.

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

Component	Description
Population	- Patients with non-familial hypercholesterolaemia and atherosclerotic cardiovascular disease who have additional risk factors and LDL levels above 2.6 mmol/L despite optimised treatment with statins and ezetimibe - Patients with familial hypercholesterolaemia and atherosclerotic cardiovascular disease who have an LDL level between 2.6 and 3.3 mmol/L despite optimised treatment with statins and ezetimibe
Intervention	Evolocumab subcutaneous injection every fortnight (140 mg) or every month (420 mg)
Comparator	- Placebo - Alirocumab subcutaneous injection every fortnight (75 to 150 mg) or every month (300 mg)
Outcomes	Reduction in LDL leading to a reduction in major cardiovascular events (e.g. cardiovascular death, myocardial infarction, stroke)
Clinical claim	- Evolocumab is superior in terms of efficacy and similar in terms of safety compared to placebo - Evolocumab is at least as effective as alirocumab (superior to alirocumab 75 mg fortnightly and 300 mg monthly and non-inferior to alirocumab 150 mg fortnightly) in terms of comparative efficacy with a similar safety profile

Source: Table 1.1.1 (p 14) of the resubmission

2 Requested listing

- 2.1 The restriction requested in the submission is outlined below. The PBAC's suggested additions are added in italics and suggested deletions are crossed out with

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strikerthrough. The ESC and the PBAC considered the proposed listing for this population to be complex.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Published (Effective) Dispensed price for maximum quantity	Proprietary name and manufacturer
EVOLOCUMAB, 140 mg/mL injection, 1 mL injection device	2	2	5	\$ [REDACTED] (\$ [REDACTED])	Repatha® Amgen
EVOLOCUMAB, 420 mg/mL injection, 3.5 mL injection device	1	1	5	\$ [REDACTED] (\$ [REDACTED])	Repatha® Amgen

Category/ Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Hypercholesterolaemia
PBS Indication:	Hypercholesterolaemia
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment phase	Initial treatment
Clinical criteria:	<p>The treatment must be in conjunction with dietary therapy and exercise AND Patient must have symptomatic atherosclerotic cardiovascular disease AND Patient must have an LDL cholesterol level in excess of 2.6 millimoles per litre</p> <p>AND Patients must have atherosclerotic disease in more than one two or more vascular territories (as per the symptomatic atherosclerotic cardiovascular disease criteria); OR Patient must have symptomatic peripheral vascular disease; OR Patient must have severe multivessel coronary heart disease defined as at least 40% 50% stenosis in at least two large vessels; OR Patient must have had at least two major cardiovascular events (i.e. myocardial infarction, unstable angina, stroke or unplanned revascularisation) in the previous 5 years; OR Patient must have had an acute coronary syndrome (i.e. myocardial infarction or unstable angina) within the previous 12 months; OR Patient must have diabetes mellitus with microalbuminuria; OR Patient must have diabetes mellitus and be aged 60 years of more; OR Patient must be an Aboriginal or Torres Strait Islander with diabetes mellitus; OR Patient must have a Thrombolysis in Myocardial Infarction (TIMI) Risk Score for Secondary Prevention (TRS2°P); of four or higher;</p> <p>AND Statin tolerant: Patient must have been treated with the maximum recommended and tolerated dose of atorvastatin or rosuvastatin according to the TGA-approved Product Information for at least 3 months in</p>

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	<p>conjunction with dietary therapy and exercise; OR</p> <p><i>Statin intolerant/contraindicated:</i> Patient must have developed clinically important product-related adverse events necessitating withdrawal of statin treatment to trials of each of atorvastatin and rosuvastatin; OR Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information,</p> <p>AND Patient must have been treated with ezetimibe for at least 3 months in conjunction with dietary therapy and exercise</p>
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<p>Treatment criteria:</p>	<p>Must be treated by or in consultation with a specialist physician.</p> <p>A clinically important product-related adverse event is defined as follows: (i) Severe myalgia (muscle symptoms without creatine kinase elevation) which is proven to be temporally associated with statin treatment; or (ii) Myositis (clinically important creatine kinase elevation, with or without muscle symptoms) demonstrated by results twice the upper limit of normal on a single reading or a rising pattern on consecutive measurements and which is unexplained by other causes; or (iii) Unexplained, persistent elevations of serum transaminases (greater than 3 times the upper limit of normal) during treatment with a statin.</p> <p>Symptomatic atherosclerotic cardiovascular disease is defined as: (i) the presence of symptomatic coronary artery disease; or (ii) the presence of symptomatic cerebrovascular disease; or (iii) the presence of symptomatic peripheral vascular disease.</p> <p>The qualifying LDL cholesterol level must be provided at the time of application and must be no more than 2 months old.</p> <p>The physician must attempt to treat the patient with the maximum recommended dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily).</p> <p>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). This retreatment should occur after a washout period of at least 1 month, or if the creatine kinase (CK) level is elevated retreatment should not occur until CK has returned to normal.</p> <p>In the event of a trial of an 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 maximum tolerated dose has been reached or target LDL-c has been achieved.</p> <p>At the time of application, one of the following must be provided:</p> <p>(i) Confirmation that the patient was treated with atorvastatin 80 mg or rosuvastatin 40 mg for 3 months; or (ii) The doses and duration of treatment and adverse events experienced with trials with each of atorvastatin and rosuvastatin; or (iii) Confirmation that the patient is contraindicated to treatment with a statin as defined in the TGA-approved Product Information.</p> <p>The authority application must be made in writing and must include: a) A completed authority prescription form; and b) A completed [insert name] Initial PBS Authority Application – Supporting Information Form; and c) The date of consultation and the full name of the consultant physician; and d) The result of LDL cholesterol level and one of the following where appropriate: statin treatment details including agent, dose and treatment duration; or details of adverse event or contraindication to treatment with a statin as defined in the TGA-approved Product Information.</p>
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<p>Prescriber Instructions</p>	<p>Symptomatic atherosclerotic cardiovascular disease is defined as:</p> <p>Symptomatic coronary artery disease (prior MI <u>or</u> prior revascularisation procedure <u>or</u> angina associated with demonstrated significant coronary artery disease ($\geq 50\%$ stenosis in ≥ 1 coronary artery on imaging <u>or</u> positive functional testing e.g. myocardial perfusion scanning or Stress Echocardiography).</p> <p>Symptomatic cerebrovascular disease (prior ischaemic stroke <u>or</u> revascularisation procedure <u>or</u> transient ischaemic attack associated with $\geq 50\%$ stenosis in ≥ 1 cerebral arteries on imaging).</p> <p>Symptomatic peripheral arterial disease (prior acute ischaemic event due to atherosclerosis <u>or</u> prior revascularisation procedure <u>or</u> symptoms of ischaemia with evidence of significant peripheral artery disease ($\geq 50\%$ stenosis in ≥ 1 peripheral artery on imaging)).</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>Symptomatic atherosclerotic cardiovascular disease is defined as:</p> <p>(i) the presence of symptomatic coronary artery disease; or</p> <p>(ii) the presence of symptomatic cerebrovascular disease; or</p> <p>(iii) the presence of symptomatic peripheral vascular disease.</p> <p>The date of the consultation with a specialist physician must be no more than 6 months prior to the application date. The full name of the specialist physician consulted and the date of consultation are to be provided at the time of application.</p> <p>The qualifying LDL cholesterol level must be provided at the time of application and must be no more than 2 months old.</p> <p>The physician must attempt to treat the patient with the maximum recommended dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily).</p> <p>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). This retrial should occur after a washout period of at least 1 month, 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 an 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 maximum tolerated dose has been reached or target LDL-c has been achieved.</p> <p>At the time of application, one of the following must be provided:</p> <p>(i) Confirmation that the patient was treated with atorvastatin 80 mg or rosuvastatin 40 mg for 3 months; or</p> <p>(ii) The doses and duration of treatment and adverse events experienced with trials with each of atorvastatin and rosuvastatin; or</p> <p>(iii) Confirmation that the patient is contraindicated to treatment with a statin as defined in the TGA-approved Product Information.</p>
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	<p>The authority application must be made in writing and must include:</p> <p>a) A completed authority prescription form; and</p> <p>b) A completed [insert name] Initial PBS Authority Application – Supporting Information Form; and</p> <p>e) a) The date of consultation and the full name of the specialist physician <i>must be recorded in the patient's medical records</i>; and</p> <p>e) b) The result of LDL cholesterol level and one of the following where appropriate: statin treatment details including agent, dose and treatment duration; or details of adverse event or contraindication to treatment with a statin as defined in the TGA-approved Product Information <i>must be recorded in the patient's medical records</i>.</p>
Notes Administrative Advice	<p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply</p> <p><i>Authority applications for initial treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</i></p> <p><i>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</i></p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>

Category/ Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Hypercholesterolaemia
PBS Indication:	Hypercholesterolaemia
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required – Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required – Electronic <input checked="" type="checkbox"/> Streamlined
Treatment phase	Continuing treatment
Clinical criteria	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND The treatment must be in conjunction with dietary therapy and exercise.

2.2 The resubmission noted that the current PBS listings for evolocumab are subject to a special pricing arrangement consisting of a ██████% rebate on government expenditure. The resubmission proposed increasing the rebate to ██████% with the requested expansion of population. This was the same level of rebate as offered in the

July 2018 submission. The pre-PBAC response further proposed increasing the rebate to ██████%.

- 2.3 The resubmission narrowed the target population to patients with atherosclerosis and additional cardiovascular risk factors (patients with multiple cardiovascular events, polyvascular disease, symptomatic peripheral vascular disease, multivessel coronary heart disease, recent acute coronary syndrome event, diabetes, Aboriginal or Torres Strait Islander), compared to previous submissions, which targeted a broader population with atherosclerosis (patients with symptomatic coronary heart disease, cerebrovascular disease, or peripheral vascular disease, and LDL-C level in excess of 3.3 mmol/L). When compared to previous submissions, the ESC considered the nominated patient subgroups to be more representative of those who would benefit most from treatment with evolocumab in the non-FH population. However, the ESC noted the following with respect to the proposed listing:

- The criteria “patient must have symptomatic atherosclerotic cardiovascular disease” has not been defined
- Polyvascular disease has not been defined
- Symptomatic peripheral vascular disease has substantial overlap with polyvascular disease
- In clinical practice, multivessel coronary heart disease is normally defined as 50% stenosis (rather than 40% as was required in the FOURIER Study)
- Prior acute coronary syndrome (ACS) within the preceding 4 weeks was excluded in FOURIER
- In the ezetimibe listing, patients with diabetes require additional risk factors, namely microalbuminuria or be aged 60 years or more
- Also in the ezetimibe listing, Aboriginal or Torres Strait Islander patients must also have the additional risk factor of diabetes

The ESC advised that the high-risk subgroups are reasonable, but that improved and more consistent definitions would be required.

- 2.4 The PBAC agreed with the issues raised by ESC in the paragraph above and also agreed with the following advice that ESC had provided regarding the proposed criteria:

i. **Patient must have symptomatic atherosclerotic cardiovascular disease:**

- The ESC and PBAC proposed the additional definitional criteria:

Symptomatic atherosclerotic cardiovascular disease is defined as:

- Symptomatic coronary artery disease (prior MI or prior revascularisation procedure or angina associated with demonstrated significant coronary artery disease ($\geq 50\%$ stenosis in ≥ 1 coronary artery on imaging or positive functional testing e.g. myocardial perfusion scanning or Stress Echocardiography)).

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- Symptomatic cerebrovascular disease (prior ischaemic stroke or revascularisation procedure or transient ischaemic attack associated with $\geq 50\%$ stenosis in ≥ 1 cerebral arteries on imaging).
 - Symptomatic peripheral arterial disease (prior acute ischaemic event due to atherosclerosis or prior revascularisation procedure or symptoms of ischaemia with evidence of significant peripheral artery disease ($\geq 50\%$ stenosis in ≥ 1 peripheral artery on imaging)).
- ii. Patients must have atherosclerotic disease in more than one vascular territory**
- The ESC and PBAC considered that polyvascular disease should be defined as two or more of the symptomatic atherosclerotic cardiovascular disease criteria in the definition above.
- iii. Patient must have symptomatic peripheral vascular disease**
- The ESC and PBAC considered this criterion to be superfluous, as it would be covered under “more than one vascular territory” in the above criteria. The ESC and PBAC suggested that it be removed from the restriction.
- iv. Patient must have severe multivessel coronary heart disease defined as at least 40% stenosis in at least two large vessels**
- The ESC and PBAC considered that ‘severe’ or high-risk multivessel coronary heart disease should be defined as at least 50% stenosis in at least two large vessels, rather than 40%. The PBAC noted that the FOURIER Trial nominated 40% as a significant stenosis.
- v. 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**
- The ESC and PBAC considered that this subgroup was appropriate.
- vi. Patient must have had an acute coronary syndrome (i.e. myocardial infarction or unstable angina) within the previous 12 months**
- The ESC and PBAC considered that this subgroup was not appropriate to include, as it was not considered sufficiently high-risk.
- vii. Patient must have diabetes mellitus**
- The ESC considered that this criterion should ideally be consistent with the ezetimibe listing, i.e. patients must have diabetes together with microalbuminuria, or have diabetes and be aged 60 years or more.

viii. Patient must be an Aboriginal or Torres Strait Islander

- The ESC and PBAC considered that this criterion should be consistent with the ezetimibe listing, i.e. patients must be an Aboriginal or Torres Strait Islander together with having diabetes.

ix. Patient must have a score of 4 or higher using the Thrombolysis in Myocardial Infarction (TIMI) risk score for secondary prevention¹

- The PBAC considered this to be an additional high-risk subgroup that would cover patients of equivalent high risk to the other subgroups, but who may not otherwise qualify. This is further discussed in Paragraph 4.4.

x. Patient must have an LDL cholesterol level in excess of 2.6 millimoles per litre

- The ESC and PBAC considered that the additional criteria for statin tolerant and statin contraindicated or intolerant should be included here, but that they should also be split across two separate PBS restrictions. The ESC and PBAC considered that the definitions should be:

Statin tolerant:

- Patient must have been treated with the maximum recommended and tolerated dose of atorvastatin or rosuvastatin according to the TGA-approved Product Information for at least 3 months in conjunction with dietary therapy and exercise; OR

Statin intolerant/contraindicated:

- Patient must have developed clinically important product-related adverse events necessitating withdrawal of statin treatment to trials of each of atorvastatin and rosuvastatin; OR
- Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information.

2.5 The pre-PBAC response accepted the revisions to the restriction proposed by the ESC in the paragraphs above.

2.6 In addition, the pre-PBAC response proposed an amendment to the definition of statin intolerance to allow access in patients who required a 'reduction in statin dose intensity' rather than complete withdrawal of statin therapy. The PBAC considered that the definition proposed by the ESC was more consistent with the existing criteria for evolocumab and would help restrict use to those patients who would benefit most from treatment with evolocumab (i.e. the PBAC considered that the definition of statin intolerant should be: 'Patient must have developed clinically important product-related adverse events necessitating withdrawal of statin treatment to trials of each of atorvastatin and rosuvastatin').

2.7 The resubmission has modified prior therapy requirements (maximum statin dose, statin intolerance, ezetimibe trial) outlined in previous submissions to be consistent

¹ <http://www.timi.org/index.php?page=trs2p>

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with the current PBS listing of evolocumab for FH. The resubmission noted that the intent of these requirements is to ensure that evolocumab is used in conjunction with the maximum tolerated dose of a statin and ezetimibe unless contraindicated.

- 2.8 The resubmission broadened the qualifying LDL threshold from 3.3 mmol/L used in the previous submissions to a 2.6 mmol/L threshold. The resubmission justified the revised threshold based on international guidelines and expert advice, which suggested that a 2.6 mmol/L threshold may represent a reasonable compromise between identifying patients who may derive the greatest benefit from PCSK9 inhibitors versus the high cost of PCSK9 inhibitors.
- 2.9 The resubmission also requested “a concurrent change to the existing heterozygous FH listing to reduce the qualifying LDL-C threshold from 3.3 mmol/L to 2.6 mmol/L”. The PBAC considered that patients with FH with symptomatic ASCVD and LDL-c levels over 2.6 mmol/L would have at least an equivalent lifetime risk as the non-FH population (with additional risk factors) identified above. The PBAC also considered that this expansion to the LDL thresholds for FH patients, if recommended, should also flow-on to the recommended PBS listing for alirocumab in he-FH.
- 2.10 The evaluation considered that the definition of each of the patient subgroups was not consistent throughout the submission (see Table 3, below) with differences likely to have a substantial impact on both the estimated baseline risk (affecting cost effectiveness) and the estimated population size of each subgroup (affecting budget impact).
- 2.11 Cardiovascular outcome data from the CTTC meta-analysis and the PCSK9 inhibitor trials indicated that patients with LDL levels between 1.8 and 2.6 mmol/L are also likely to benefit from treatment. The Commentary considered that, as a consequence there remains a risk of leakage outside the restriction for patients who are not able to achieve target LDL thresholds with available treatments (current treatment guidelines recommend a target of < 1.8 mmol/L in patients with atherosclerotic disease) but who do not meet the PBS-criteria for evolocumab. The ESC agreed with the Commentary and noted a potential gap exists for individuals who fail to achieve target LDL on a maximum tolerated dose statin and trial of ezetimibe, but who are not eligible for evolocumab. However, the ESC considered that if leakage to this group of patients did occur, it would most likely be in clinically identified higher-risk patients.
- 2.12 The pre-PBAC response acknowledged that, given the expectant patient volume, a written initial Authority would not be feasible and accepted that a telephone/electronic Authority would be a more practical alternative from an implementation perspective. The PBAC considered that a telephone/electronic initial Authority would be appropriate, provided the specific entry criteria is explicitly addressed and the prescriber is told to retain the relevant documentation.

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

3 Background

Registration status

- 3.1 Evolocumab was first registered by the TGA in December 2015 for treatment of primary hypercholesterolaemia and homozygous FH. The TGA indication was later revised in August 2018 to include the prevention of cardiovascular events.
- 3.2 The current TGA approved indication for evolocumab is:
- 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

- 3.3 The outstanding matters of concern from the previous July 2018 PBAC meeting are summarised in the table below.

Table 2: Summary of outstanding matters of concern

Matter of concern	How the resubmission addresses it
The PBAC considered that the population subgroups that would most benefit from treatment were inadequately defined [7.2 July 2018 evolocumab PSD]. The PBAC considered that LDL was possibly not the best way to select the highest risk group and suggested that the ICER should be modelled for high-risk populations using different risk factors such as recent MI or MI with high LDL, multiple previous cardiovascular events, multi-vessel coronary artery disease, etc., to allow the determination of a cost effective population. [7.3 July 2018 evolocumab PSD]	The target population was revised to identify subgroups based on cardiovascular risk factors (patients with multiple cardiovascular events, polyvascular disease, multivessel coronary heart disease, Aboriginal or Torres Strait Islanders with diabetes).
For non-familial hypercholesterolaemia, the PBAC was concerned that by nominating ezetimibe as a comparator, it would be replaced in the treatment algorithm by evolocumab [7.3 July 2018 evolocumab PSD].	The nominated comparator was changed to placebo with the clinical management algorithm indicating that evolocumab should be used after ezetimibe treatment.

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Matter of concern	How the resubmission addresses it
<p>The PBAC considered that for patients intolerant to statins, the restriction should be amended to include a trial of ezetimibe treatment. In addition, for patients who can tolerate statins and/or ezetimibe, the PBAC considered that treatment with evolocumab must be in conjunction with the maximum tolerated dose of a HMG CoA reductase inhibitor and ezetimibe unless contraindicated [7.5 July 2018 evolocumab PSD].</p>	<p>The resubmission modified prior therapy requirements (maximum statin dose, statin intolerance, ezetimibe trial) outlined in previous submissions to be consistent with the current PBS listing of evolocumab for familial hypercholesterolaemia.</p>
<p>The PBAC considered that the nominated qualifying LDL threshold of 3.3 mmol/L in the evolocumab restriction was arbitrary in the context of secondary prevention in the population with non-FH with atherosclerotic cardiovascular disease [7.5 July 2018 evolocumab PSD].</p>	<p>The resubmission broadened the qualifying LDL threshold 2.6 mmol/L. The resubmission justified the revised threshold based on international guidelines and expert advice, which suggested that this threshold may represent a reasonable compromise between identifying all patients who may benefit from PCSK9 inhibitors versus the high cost of PCSK9 inhibitors.</p>
<p>The PBAC considered that, while the weight of evidence with LDL-c lowering would be associated with a reduction in cardiovascular mortality, there was no direct data from the FOURIER trial to support the length of the time lag or the magnitude of the reduction in cardiovascular mortality in secondary prevention of coronary artery disease with evolocumab. The PBAC noted that this was a key driver of the economic model [7.6 July 2018 evolocumab PSD].</p>	<p>The resubmission revised the estimate of mortality lag from 3.6 years used in previous submission to a 2 year lag with a linear progression to maximum treatment effect over the next 2 years. The resubmission argued that the revised mortality lag approach corresponds to the observed lag in treatment effect on cardiovascular mortality in the statin and alirocumab studies and also corresponds more directly to the likely mechanism of plaque stabilisation and reduction increasing over time than the previous ‘all-or-nothing’ approach. The pre-PBAC response revised base case used a 3.6 year mortality lag, per the previous submission.</p>
<p>The PBAC reiterated its previous recommendation that the FOURIER trial data could be used to better inform the economic model [7.7 July 2018 evolocumab PSD]</p>	<p>The resubmission disagreed that FOURIER patients are representative of the real-world patients who will receive PBS subsidised evolocumab, particularly the high-risk subpopulation proposed for listing. Therefore, the resubmission derived baseline risks and distribution of cardiovascular events based on sponsor-commissioned analysis of Swedish registry data.</p> <p>The Commentary and ESC considered that the FOURIER trial appeared to remain the best available source of data for the Australian PBS population, particularly for high cardiovascular risk subgroups. Thus, the PSCR and pre-PBAC response updated the model to be based on the FOURIER trial data (adjusted for higher risk subgroups and higher baseline LDL-c).</p>
<p>The PBAC considered that while the 35-year time horizon may be reasonable, a 25 year time horizon including reduced effectiveness and compliance over time may be informative, considering the mean age of patients in the model was 64 years [7.7 July 2018 evolocumab PSD].</p>	<p>There were no changes to time horizon or treatment compliance in the economic model presented in the resubmission. The pre-PBAC revised base case used a 25 year time horizon and assumed 1% of patients discontinue treatment each monthly cycle for the first 4 years.</p>
<p>The PBAC noted that the financial impact of listing evolocumab in patients with non-familial hypercholesterolemia was very high with significant uncertainties regarding the size of the population meeting the eligibility criteria, market growth rates, uptake rates and cost offsets related to statin and ezetimibe use [7.8 July 2018 evolocumab PSD].</p>	<p>The resubmission provided revised budget impact estimates for third-line treatment (after statin and ezetimibe) with evolocumab in high-risk subgroups.</p>

Source: Table 1.1-6 (p 18) of the resubmission

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 major impact on survival, quality of life and future risk of further cardiovascular events.
- 4.3 The resubmission identified eight different subgroups of patients with hypercholesterolaemia and atherosclerotic disease who have a very high risk of a future cardiovascular event. The resubmission positioned evolocumab as a treatment option in patients with LDL levels above 2.6 mmol/L, despite optimised treatment with statins and ezetimibe.

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Table 3: Subgroup definitions, prevalence and baseline risk used in the resubmission

Subgroup	Restriction	FOURIER ^a	Economic model	Budget impact ^b
Multiple events	Definition: Patients with multiple coronary vascular events (i.e. myocardial infarction, unstable angina, stroke or unplanned revascularisation) in previous 5 years	Definition: Patients with multiple myocardial infarctions at any time Baseline risk: 0.064 events per subject year (0.042 x 1.515) Prevalence: 19.17% (5,285 / 27,564)	Definition: Patients with multiple myocardial infarctions at any time Baseline risk: 0.095 events per subject year (0.063 x 1.515)	Definition: Patients with stroke who have a prior history of transient ischaemic attack or stroke at any time; Patients with myocardial infarction or unstable angina who have a prior history of multiple MI events at any time Prevalence: 17.11% (50,821 / 296,973)
Polyvascular disease	Definition: Patients with atherosclerosis in more than one vascular territory	Definition: Patients with atherosclerosis in more than one vascular territory (identified during evaluation) Baseline risk: 0.071 events per subject year (0.042 x 1.687) Prevalence: 12.93% (3,563 / 27,564)	Definition: Patients with atherosclerosis in more than one vascular territory (identified during evaluation) Baseline risk: 0.106 events per subject year (0.063 x 1.687)	Definition: Not defined Prevalence: Not reported
Multivessel disease	Definition: Atherosclerosis patients who have ≥ 40% stenosis in ≥ 2 large vessels	Definition: Patients with myocardial infarction who have ≥ 40% stenosis in ≥ 2 large vessels Baseline risk: 0.053 events per subject year (0.042 x 1.273) Prevalence: 20.38% (5,618 / 27,564)	Definition: Patients with myocardial infarction who have ≥ 40% stenosis in ≥ 2 large vessels Baseline risk: 0.080 events per subject year (0.063 x 1.273)	Definition: Patients with myocardial infarction or unstable angina who have ≥ 40% stenosis in ≥ 2 large vessels Prevalence: 13.82% (41,028 / 296,973)
Recent event in previous year	Definition: Patients with an acute coronary syndrome (i.e. myocardial infarction or unstable angina) within the previous 12 months	Definition: Patients with a myocardial infarction within the previous 12 months Baseline risk: 0.046 events per subject year (0.042 x 1.101) Prevalence: 20.72% (5,711 / 27,564)	Definition: Patients with a myocardial infarction within the previous 12 months Baseline risk: 0.069 events per subject year (0.063 x 1.101)	Definition: Patients with an acute coronary syndrome (i.e. myocardial infarction or unstable angina) within the previous 12 months Prevalence: 14.38% (42,699 / 296,973)
Peripheral vascular disease	Definition: Patients with symptomatic peripheral vascular disease	Definition: Patients with symptomatic peripheral arterial disease Baseline risk: 0.064 events per subject year (0.042 x 1.535) Prevalence: 13.21% (3,642 / 27,564)	Definition: Patients with symptomatic peripheral arterial disease Baseline risk: 0.097 events per subject year (0.063 x 1.535)	Definition: Patients with symptomatic peripheral arterial disease Prevalence: 10.11% (30,023 / 296,973)

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Subgroup	Restriction	FOURIER ^a	Economic model	Budget impact ^b
Diabetes	Definition: Atherosclerosis patients with diabetes	Definition: Atherosclerosis patients with diabetes Baseline risk: 0.052 events per subject year (0.042 x 1.232) Prevalence: 40.02% (11,031 / 27,564)	Definition: Atherosclerosis patients with diabetes Baseline risk: 0.078 events per subject year (0.063 x 1.232)	Definition: Atherosclerosis patients with diabetes Prevalence: 30.00% (89,092 / 296,973)
Aboriginal or Torres Strait Islander	Definition: Aboriginal or Torres Strait Islanders with atherosclerotic cardiovascular disease	Definition: Not defined Baseline risk: Not reported Prevalence: Not reported	Definition: Not defined Baseline risk: Not reported	Definition: Aboriginal or Torres Strait Islanders with atherosclerotic cardiovascular disease Prevalence: 2.80% (8,315 / 296,973)
Familial disease	Definition: Patients with familial hypercholesterolaemia and LDL levels between 2.6 and 3.3 mmol/L	Definition: Not defined Baseline risk: Not reported Prevalence: Not reported	Definition: Not defined Baseline risk: Not reported	Definition: Patients with familial hypercholesterolaemia and LDL levels between 2.6 and 3.3 mmol/L Prevalence: 4.66% (14,513 / 311,485)

Source: Bonaca et al (2018) PAD publication; Sabatine et al (2017) main publication; Sabatine et al (2017) diabetes publication; Sabatine et al (2018) severe CAD publication; Tables 14-4.6.17 to 14-4.6.32 of the FOURIER trial report

^a Baseline risk estimates are based on the secondary composite outcome of cardiovascular death, myocardial infarction, or stroke

^b Prevalence estimates used in the budget impact are based on overlap unrestricted estimates for Year 1 population values

- 4.4 During the evaluation, it was noted that the draft Australian consensus document on the status of PCSK9 monoclonal antibody inhibitors in Australia identified an alternative measure of assessing cardiovascular risk based on the Thrombolysis in Myocardial Infarction (TIMI) risk score for Secondary Prevention (draft manuscript provided in the resubmission – Appendix 1). The TIMI risk score was originally developed as a 0-9 point scale based on the presence or absence of 9 cardiovascular risk factors in patients with a prior myocardial infarction (age ≥ 75 years, diabetes mellitus, hypertension, current smoking, peripheral artery disease, prior stroke, prior coronary artery bypass grafting, history of heart failure, and renal dysfunction (eGFR < 60 mL/min/1.73m²). This 9-point scale was externally validated in a number of settings and was used in post-hoc analyses of the IMPROVE-IT trial (high risk: > 3 points). Overall, the evaluation, ESC and PBAC considered that the TIMI risk score would be a viable approach to identifying a high-risk patient subgroup suitable for treatment with PCSK9 inhibitors. The evaluation noted that a modified version that uses a 0-10 scale, which includes prior myocardial infarction as a cardiovascular risk factor, had also been published and was used in post-hoc analyses of the FOURIER trial (high risk ≥ 5 points).
- 4.5 The Pre-Sub-Committee Response (PSCR) claimed that use of a risk scoring system could be more problematic and susceptible to leakage than the use of objective clinical measures as proposed in the submission. The ESC advised that there would be appropriately high-risk populations identified by the TIMI score that may not otherwise qualify under the proposed PBS listing. The ESC and PBAC considered that a combination of the two, i.e. the addition of the TIMI score to the nominated high-risk groups, would be appropriate and may best allow therapy targeted to the highest risk groups.

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

5 Comparator

- 5.1 The resubmission claimed that evolocumab would be used in addition to optimised background treatment (with statins and ezetimibe), and therefore nominated placebo as the main comparator. The ESC considered this comparator appropriate.
- 5.2 The resubmission also nominated alirocumab as a near market comparator on the basis that it is a similar agent to evolocumab (same drug class) which had previously been considered by the PBAC for similar indications. However, the PBAC recalled that, in March 2019, it did not recommend the listing of alirocumab for patients with non-FH (and other risk factors), and as such considered that alirocumab was not a relevant comparator in this case.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (2), health care professionals (6) and an organisation (1). The comments described the benefits of treatment with evolocumab, particularly for secondary cardiovascular prevention in patients with persistently raised LDL cholesterol and for those who cannot use statins, as well as for FH patients who do not qualify under the current PBS listing. The comments described evolocumab as being well tolerated and leading to significant reductions in LDL-c levels.

Clinical trials

6.3 The resubmission was based on a series of comparisons between evolocumab and nominated comparators:

- One head-to-head comparison of cardiovascular outcomes with evolocumab versus placebo in hypercholesterolaemia patients with atherosclerotic cardiovascular disease (FOURIER), including additional subgroup analyses based on cardiovascular risk factors. Data from the subgroup analyses have not previously been considered by the PBAC.
- Indirect comparisons of lipid outcomes with evolocumab versus alirocumab in various hypercholesterolaemia populations (ANITSCHKOW, BANTING, BERSON, DESCARTES, FOURIER, GAUSS-1, GAUSS-2, GAUSS-3, GAUSS-4, GLAGOV, LAPLACE-1, LAPLACE-2, MENDEL-1, MENDEL-2, RUTHERFORD-1, RUTHERFORD-2, YUKAWA-1, YUKAWA-2, McKenney 2012, Roth 2012, Stein 2012, Teramoto 2016, ODYSSEY ALTERNATIVE, ODYSSEY CHOICE I, ODYSSEY CHOICE II, ODYSSEY COMBO I, ODYSSEY COMBO II, ODYSSEY DM DYSLIPIDEMIA, ODYSSEY DM INSULIN, ODYSSEY FH I, ODYSSEY FH II, ODYSSEY FH HIGH RISK, ODYSSEY JAPAN, ODYSSEY KT, ODYSSEY LONG TERM, ODYSSEY MONO, ODYSSEY NIPPON, ODYSSEY OPTIONS I, ODYSSEY OPTIONS 2). Data from the ANITSCHKOW, BANTING, BERSON, GAUSS-4, ODYSSEY DM INSULIN, ODYSSEY DM DYSLIPIDEMIA, ODYSSEY KT and ODYSSEY NIPPON trials have not previously been considered by the PBAC.

6.4 The resubmission did not present any specific clinical data to support the use of evolocumab in Aboriginal and Torres Strait Islanders or the proposed extension of listing for FH in patients with atherosclerotic disease who have an LDL level between 2.6 and 3.3 mmol/L. The ESC noted that this proposed extension to the familial

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hypercholesterolaemia (FH) population could equally have been achieved by listing FH as a high-risk subgroup in the current submission for ASCVD.

6.5 The resubmission also argued that it was not appropriate to conduct an indirect analysis of cardiovascular outcomes between evolocumab and alirocumab due to the differences in patient populations, study design, outcome definitions and duration of follow-up between the FOURIER and ODYSSEY OUTCOMES trials.

6.6 Details of the trials presented in the submission are provided in the table below.

Table 4: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Evolocumab clinical trials		
20130293 (ANITSCHKOW)	A Randomized Double-blind Placebo Controlled Study Characterizing The Effects of PCSK9 Inhibition On Arterial Wall Inflammation in Patients With Elevated Lp(a) (ANITSCHKOW)	September 2018
20130287 (BANTING)	A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy of Evolocumab (AMG 145) on LDL-C in Subjects With Type 2 Diabetes Mellitus and Hypercholesterolaemia/Mixed Dyslipidemia (BANTING)	January 2018
20120119 (BERSON)	A Double-blind, Randomized, Placebo-Controlled, Multicenter Study to Evaluate Safety and Efficacy of AMG 145 in Combination With Statin Therapy in Diabetic Subjects With Hyperlipidemia or Mixed Dyslipidemia (BERSON)	June 2018
	Lorenzatti AJ et al. Rationale and design of a randomized study to assess the efficacy and safety of evolocumab in patients with diabetes and dyslipidemia: The BERSON clinical trial	Clin Cardiol 2018; 41: 1117–1122.
	Lorenzatti AJ et al. Randomised study of evolocumab in patients with type 2 diabetes and dyslipidaemia on background statin: Primary results of the BERSON clinical trial	Diabetes Obes Metab (ahead of print March 2019): https://doi.org/10.1111/DOM.13680
20110109 (DESCARTES)	A Double-blind, Randomised, Placebo-controlled, Multicenter Study to Evaluate Long-term Tolerability and Durable Efficacy of AMG 145 on LDL-C in Hyperlipidemic Subjects	June 2014
	Blom D et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia.	N Engl J Med 2014; 370:1809–1819.
	Blom D et al. Effects of Evolocumab on Vitamin E and Steroid Hormone Levels Results From the 52-Week, Phase 3, Double-Blind, Randomised, Placebo-Controlled DESCARTES Study	Circ Res 2015; 117:731–741.
	Blom D et al. Evaluation of the Efficacy, Safety, and Glycaemic Effects of Evolocumab (AMG 145) in Hypercholesterolaemic Patients Stratified by Glycaemic Status and Metabolic Syndrome	Diabetes Obes Metab 2017; 19(1): 98–107.
20110118 (FOURIER)	A Double-blind, Randomised, Placebo-controlled, Multicenter Study Assessing the Impact of Additional LDL-Cholesterol Reduction on Major Cardiovascular Events When AMG 145 is Used in Combination With Statin Therapy in Patients with Clinically Evident Cardiovascular Disease	April 2017
	Sabatine MS et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease	N Engl J Med 2017; 376(18): 1713–1722.
	Sabatine MS et al. Rationale and design of the Further cardiovascular Outcomes Research with PCSK9 Inhibition in subjects with Elevated Risk trial	American Heart J 2015; 173: 94-101.
	Sabatine MS et al. Clinical Benefit of Evolocumab by Severity and Extent of Coronary Artery Disease	Circulation 2018; 138(8); 756–766.

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Trial ID	Protocol title/ Publication title	Publication citation
	Giugliano RP et al. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial	Lancet 2017; 390: 1962–1971.
	Giugliano RP et al. Clinical efficacy and safety of evolocumab in high-risk patients receiving a statin: secondary analysis of patients with low LDL cholesterol levels and in those already receiving a maximal-potency statin in a randomized clinical trial	JAMA Cardiol 2017; 2(12): 1385–1391.
	Bonaca MP et al. Low-Density Lipoprotein Cholesterol Lowering with Evolocumab and Outcomes in Patients with Peripheral Artery Disease: Insights from the FOURIER Trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk)	Circulation 2018; 137(4): 338–350.
	Sabatine MS et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial	Lancet Diabetes Endoc 2017; 5(12): 941–950.
	Qamar A et al. Interindividual Variation in Low-Density Lipoprotein Cholesterol Level Reduction with Evolocumab: An Analysis of FOURIER Trial Data	JAMA Cardiol 2019; 4(1): 59–63.
20090159 (GAUSS-1)	A Randomised, Multicenter Study to Evaluate Tolerability and Efficacy of AMG 145 on LDL-C, Compared with Ezetimibe, in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor (GAUSS: Goal Achievement after Utilising an anti-PCSK9 antibody in Statin Intolerant Subjects)	October 2012
	Sullivan D et al. Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: The GAUSS randomized trial	JAMA 2012; 308(23): 2497–2506.
20110116 (GAUSS-2)	A Double-blind, Randomised, Multicenter Study to Evaluate Safety and Efficacy of AMG 145, Compared With Ezetimibe, in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor	April 2014
	Cho L et al. Design and rationale of the GAUSS-2 study trial: A double-blind, ezetimibe-controlled phase 3 study of the efficacy and tolerability of evolocumab (AMG 145) in subjects with hypercholesterolaemia who are intolerant of statin therapy	Clin Cardiol 2014; 37(3): 131–139.
	Cho L et al. Clinical profile of statin intolerance in the Phase 3 GAUSS-2 study	Cardiovasc Drugs Ther 2016; 30: 297–304
	Stroes E et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: The GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab	JACC 2014; 63(23): 2541–2548.
20120332 (GAUSS-3)	A Double-blind, Randomised, Multicenter Study to Evaluate the Safety and Efficacy of AMG 145, Compared With Ezetimibe, in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor Due to Muscle Related Side Effects	June 2016
	Nissen SE et al. Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance. The GAUSS-3 randomised clinical trial	JAMA 2016; 315(15): 1580–1590.
20140234 (GAUSS-4)	A Double-blind, Randomized, Multicenter Study to Evaluate the Safety and Efficacy of Evolocumab, Compared With Ezetimibe, in Hypercholesterolemic Japanese Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor Due to Muscle Related Side Effects (GAUSS-4: Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects) – Final Analysis Report	October 2018

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Trial ID	Protocol title/ Publication title	Publication citation
20120153 (GLAGOV)	A Randomised, Multi-center, Placebo-controlled, Parallel Group Study to Determine the Effects of AMG 145 Treatment on Atherosclerotic Disease Burden As Measured By Intravascular Ultrasound in Subjects Undergoing Coronary Catheterisation	December 2016
	Nicholls SJ et al. Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients. The GLAGOV Randomised Clinical Trial	JAMA 2016; 316(22): 2373–2384.
	Puri R et al. Impact of PCSK9 inhibition on coronary atheroma progression: Rationale and design of Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV)	Am Heart J 2016 176: 83–92.
	Nissen S and Nichols SJ. Results of the GLAGOV trial	Cleveland Clinic J Med 2017; 84(12): e1-e5.
20101155 (LAPLACE-TIMI 57)	A Double-blind, Randomized, Placebo-controlled, Multicenter, Dose-ranging Study to Evaluate Tolerability and Efficacy of AMG 145 on LDL-C in Combination with HMG-CoA Reductase Inhibitors in Hypercholesterolemic Subjects (LAPLACE: LDL-C Assessment w/ PCSK9 monoclonal antibody inhibition combined with statin therapy)	April 2013
	Desai NR et al. AMG145, a monoclonal antibody against proprotein convertase subtilisin kexin type 9, significantly reduces lipoprotein(a) in hypercholesterolemic patients receiving statin therapy: An analysis from the LDL-C assessment with proprotein convertase subtilisin kexin type 9 monoclonal antibody inhibition combined with statin therapy (LAPLACE)-thrombolysis in myocardial infarction (TIMI) 57 Trial	Circulation 2013; 128: 962–969.
	Desai NR et al. AMG 145, a monoclonal antibody against PCSK9, facilitates achievement of national cholesterol education program-adult treatment panel III low-density lipoprotein cholesterol goals among high-risk patients: An analysis from the LAPLACE-TIMI 57 trial (LDL-C assessment with PCSK9 monoclonal antibody inhibition combined with statin therapy-thrombolysis in myocardial infarction 57)	JACC 2014; 63(5): 430-433.
	Giugliano R et al. Efficacy, safety and tolerability of a monoclonal antibody to protein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study.	Lancet 2012; 380(9838): 2007–2017.
20110115 (LAPLACE-2)	A Double-blind, Randomised, Placebo and Ezetimibe Controlled, Multicentre Study to Evaluate Safety, Tolerability and Efficacy of AMG 145 on LDL-C in Combination with Statin Therapy in Subjects with Primary hypercholesterolaemia and Mixed Dyslipidemia.	April 2014
	Robinson JG et al. Effect of evolocumab or ezetimibe added to moderate-Or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolaemia: The LAPLACE-2 randomized clinical trial	JAMA 2014; 311(18): 1870–1882.
	Robinson JG et al. Rationale and design of LAPLACE-2: A phase 3, randomized, double-blind, placebo- and ezetimibe-controlled trial evaluating the efficacy and safety of evolocumab in subjects with hypercholesterolaemia on background statin therapy	Clin Cardiol 2014; 37(4): 195–203.
20101154 (MENDEL-1)	A Randomised, Placebo- and Ezetimibe-controlled, Dose-ranging Study to Evaluate Tolerability and Efficacy of AMG 145 on LDL-C in Hypercholesterolemic Subjects With a 10-year Framingham Risk Score of 10% or Less (MENDEL-1: Monoclonal antibody against PCSK9 to reduce Elevated LDL-C in subjects currently Not receiving Drug therapy for Easing Lipid levels)	August 2012

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Trial ID	Protocol title/ Publication title	Publication citation
	Koren M et al. Efficacy, safety and tolerability of a monoclonal antibody to protein convertase subtilisin/kexin type 9 as monotherapy in patients with hypercholesterolaemia (MENDEL-1): a randomised, double-blind, placebo-controlled, phase 2 study.	Lancet 2012; 380(9838):1995–2006.
	Peach M et al. Effect of evolocumab on cholesterol synthesis and absorption.	J Lipid Res 2016; 57: 2217–2224.
20110114 (MENDEL-2)	A Double-blind, Randomised, Placebo and Ezetimibe-controlled, Multicenter Study to Evaluate Safety and Efficacy of Lipid Lowering Monotherapy With AMG 145 in Subjects With a 10-Year Framingham Risk Score of 10% or Less	March 2014
	Koren MJ et al. Anti-PCSK9 monotherapy for hypercholesterolaemia: The MENDEL-2 randomized, controlled phase III clinical trial of evolocumab	JACC 2014; 63: 2531–2540.
20090158 (RUTHERFORD-1)	A Double-blind, Randomised, Placebo-controlled, Multicenter Study to Evaluate Tolerability and Efficacy of AMG 145 on LDL-C in Subjects with Heterozygous Familial hypercholesterolaemia	September 2012
	Raal F et al (2012). Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolaemia: The reduction of LDL-C with PCSK9 inhibition in heterozygous familial hypercholesterolaemia disorder (RUTHERFORD) randomized trial	Circulation 126(20): 2408–2417.
20110117 (RUTHERFORD-2)	A double-blind, randomised, placebo-controlled, multicentre study to evaluate safety, tolerability and efficacy of AMG 145 on LDL-C in subjects with heterozygous familial hypercholesterolaemia.	April 2014
	Raal F et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial.	Lancet 2015; 385(9965): 331–340.
	Dent R et al. Evolocumab lowers LDL-C safely and effectively when self-administered in the at-home setting	SpringerPlus 2016; 5: 300.
20110231 (YUKAWA-1)	A Double-blind, Randomised, Placebo-controlled, Multicenter Study to Evaluate Tolerability and Efficacy of AMG 145 on LDL-C in Combination With Stable Statin Therapy in Japanese Subjects With Hypercholesterolaemia and High Cardiovascular Risk	October 2013
	Hirayama A et al. Effects of evolocumab (AMG 145), a monoclonal antibody to PCSK9, in hypercholesterolemic, statin-treated Japanese patients at high cardiovascular risk - Primary results from the phase 2 YUKAWA study	Circulation J 2014; 78: 1073–1082.
20120122 (YUKAWA-2)	A Double-blind, Randomised, Placebo-Controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of AMG 145 on LDL-C in Combination With Statin Therapy in Japanese Subjects With High Cardiovascular Risk and With Hyperlipidemia or Mixed Dyslipidemia (YUKAWA-2)	November 2014
	Kiyosue A et al. A Phase 3 Study of Evolocumab (AMG 145) in Statin-Treated Japanese Patients at High Cardiovascular Risk	Am J Cardiol 2016; 117: 40–47
Alirocumab clinical trials		
McKenney (2012)	McKenney JM et al. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolaemia receiving ongoing stable atorvastatin therapy	JACC 2012; 59: 2344–2353.
ODYSSEY ALTERNATIVE	Moriarty P et al. Efficacy and safety of alirocumab versus ezetimibe in statin-intolerant patients, with a statin-re-challenge arm: The ODYSSEY ALTERNATIVE randomized trial.	J Clin Lipidol 2015; 9: 758–769.
ODYSSEY CHOICE I	Roth EM et al. A phase III randomized trial evaluating alirocumab 300 mg every 4 weeks as monotherapy or add-on to statin: ODYSSEY CHOICE I	Atherosclerosis 2016; 254: 254–262.

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Trial ID	Protocol title/ Publication title	Publication citation
ODYSSEY CHOICE II	Stroes E et al. Efficacy and Safety of Alirocumab 150 mg Every 4 Weeks in Patients With Hypercholesterolaemia Not on Statin Therapy: The ODYSSEY CHOICE II Study	J Am Heart Assoc 2016; 5(9): e003421.
ODYSSEY COMBO I	Kereiakes D et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: The ODYSSEY COMBO I study	Am Heart J 2015; 169: 906–915.
	Colhoun HM et al. Efficacy and safety of alirocumab, a fully human PCSK9 monoclonal antibody, in high cardiovascular risk patients with poorly controlled hypercholesterolemia on maximally tolerated doses of statins: rationale and design of the ODYSSEY COMBO I and II trials.	BMC Cardiovascular Disorders 2014, 14:121
ODYSSEY COMBO II	Cannon CP et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial	Eur Heart J 2015; 36: 1186–1194.
	Colhoun HM et al. Efficacy and safety of alirocumab, a fully human PCSK9 monoclonal antibody, in high cardiovascular risk patients with poorly controlled hypercholesterolemia on maximally tolerated doses of statins: rationale and design of the ODYSSEY COMBO I and II trials	BMC Cardiovascular Disorders 2014, 14:121
	El Shahawy M et al. Efficacy and Safety of Alirocumab Versus Ezetimibe Over 2 Years (from ODYSSEY COMBO II)	Am J Cardiol 2017; 120(6): 931–939.
	Leiter LA et al. Lipid-lowering efficacy and safety of alirocumab in patients with or without diabetes: a sub-analysis of ODYSSEY COMBO II	Diabetes Obes Metab 2017; 19: 989–996.
ODYSSEY DM - INSULIN	A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab in Insulin Treated Patients With Type 1 or Type 2 Diabetes and With Hypercholesterolaemia at High Cardiovascular Risk Not Adequately Controlled on Maximally Tolerated LDL-C Lowering Therapy	Clinicaltrials.gov, NCT02585778
	Cariou, B et al. Efficacy and safety of alirocumab in insulin-treated patients with type 1 or type 2 diabetes and high cardiovascular risk: Rationale and design of the ODYSSEY DM-INSULIN trial	Diab & Metab 2017; 43: 453–359.
	Leiter LA et al. Efficacy and safety of alirocumab in insulin-treated individuals with type 1 or type 2 diabetes and high cardiovascular risk: The ODYSSEY DM-INSULIN randomized trial	Diabetes Obes Metab 2017; 19(12): 1781–1792.
ODYSSEY DM-DYSLIPIDEMIA	A Randomized, Open-Label, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab Versus Usual Care in Patients With Type 2 Diabetes and Mixed Dyslipidemia at High Cardiovascular Risk With Non-HDL-C Not Adequately Controlled With Maximally Tolerated Statin Therapy	Clinicaltrials.gov, NCT02642159
	Ray KK et al. Alirocumab vs usual lipid-lowering care as add-on to statin therapy in individuals with type 2 diabetes and mixed dyslipidaemia: The ODYSSEY DM-DYSLIPIDEMIA randomized trial	Diabetes Obes Metab 2018; 20: 1479–1489.
	Müller-Weiland et al. Design and rationale of the ODYSSEY DM-DYSLIPIDEMIA trial: lipid-lowering efficacy and safety of alirocumab in individuals with type 2 diabetes and mixed dyslipidaemia at high cardiovascular risk	Cardiovasc Diabetol 2017; 16: 70.
ODYSSEY FH I	Kastelein J et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia.	Eur Heart J 2015; 36: 2996-3003.
ODYSSEY FH II	Kastelein J et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia.	Eur Heart J 2015; 36: 2996-3003.
ODYSSEY FH HIGHRISK	Ginsberg HN et al. Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial Hypercholesterolaemia and LDL-C of 160 mg/dl or Higher	Cardiovasc Drugs Ther 2016; 30: 473–483.

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Trial ID	Protocol title/ Publication title	Publication citation
ODYSSEY JAPAN	Teramoto T et al. Efficacy and Safety of Alirocumab in Japanese Patients With Heterozygous Familial Hypercholesterolaemia or at High Cardiovascular Risk With Hypercholesterolaemia Not Adequately Controlled With Statins – ODYSSEY JAPAN Randomized Controlled Trial	Circ J 2016; 80: 1980–1987.
	Teramoto T et al. Efficacy and safety of alirocumab in Japanese patients with diabetes mellitus: Post-hoc subanalysis of ODYSSEY JAPAN	J Atheroscler Thromb 2019; 26: 282–293.
ODYSSEY KT	A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab in High Cardiovascular Risk Patients With Hypercholesterolaemia Not Adequately Controlled With Their Lipid-Modifying Therapy in South Korea and Taiwan	Clinicaltrials.gov, NCT02289963
	Koh KK et al. A randomized trial evaluating the efficacy and safety of alirocumab in South Korea and Taiwan (ODYSSEY KT)	J Clin Lipidol 2018; 12: 162–172.
	Nam C-W et al. Efficacy and safety of alirocumab in Korean patients with hypercholesterolemia and high cardiovascular risk: subanalysis of the ODYSSEY-KT study	Korean J Intern Med 2018; epub ahead of print. https://doi.org/10.3904/kjim.2018.133
ODYSSEY LONG TERM	Robinson JG et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events.	N Engl J Med 2015; 372: 1489–1499.
	Dofour R et al. Individualized low-density lipoprotein cholesterol reduction with alirocumab titration strategy in heterozygous familial hypercholesterolemia: Results from an open-label extension of the ODYSSEY LONG TERM trial.	J Clin Lipidol 2019; 13: 138–147.
	M-R Taskinen et al. Efficacy and safety of alirocumab in individuals with type 2 diabetes mellitus with or without mixed dyslipidaemia: Analysis of the ODYSSEY LONG TERM trial.	Atherosclerosis 2018; 276: 124 –130.
ODYSSEY MONO	Roth EM et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolaemia: Results of a 24 week, double-blind, randomized Phase 3 trial	Int J Cardiol 2014; 176: 55–61.
ODYSSEY NIPPON	A Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab in Patients With Hypercholesterolaemia Not Adequately Controlled With Non-statin Lipid Modifying Therapy or the Lowest Strength of Statin	Clinicaltrials.gov, NCT02584504
	Teramoto T et al. Efficacy and safety of alirocumab 150 mg every 4 weeks in hypercholesterolemic patients on non-statin lipid-lowering therapy or lowest strength dose of statin: ODYSSEY NIPPON.	J Cardiol 2019; 73: 218–227.
ODYSSEY OPTIONS I	Bays H et al. Alirocumab as add-on To atorvastatin versus other lipid treatment strategies: ODYSSEY OPTIONS I randomized trial	J Clin Endocrinol Metab 2015; 100(8): 3140–3148.
	Robinson JG et al. Efficacy and safety of alirocumab as add-on therapy in high-cardiovascular-risk patients with hypercholesterolemia not adequately controlled with atorvastatin (20 or 40 mg) or rosuvastatin (10 or 20mg): Design and rationale of the ODYSSEY OPTIONS studies.	Clin Cardiol 2014, 37(10):597–604.
ODYSSEY OPTIONS II	Farnier M et al. Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular-risk patients: The ODYSSEY OPTIONS II randomized trial.	Atherosclerosis 2016; 244: 138–46.
	Robinson JG et al. Efficacy and safety of alirocumab as add-on therapy in high-cardiovascular-risk patients with hypercholesterolemia not adequately controlled with atorvastatin (20 or 40 mg) or rosuvastatin (10 or 20mg): Design and rationale of the ODYSSEY OPTIONS studies.	Clin Cardiol 2014, 37(10):597–604.
ODYSSEY OUTCOMES	Schwartz G et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome.	N Engl J Med 2018; 379:2097–2107.
	Schwartz G et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: Rationale and design of the ODYSSEY Outcomes trial.	Am Heart J 2014; 168: 682–689.

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Trial ID	Protocol title/ Publication title	Publication citation
	Szarek M et al. Alirocumab reduces total nonfatal cardiovascular and fatal events: The ODYSSEY OUTCOMES trial.	JACC 2019; 73(4): 387– 396.
Roth (2012)	Roth EM et al. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolaemia.	N Engl J Med 2012; 367: 1891–1900.
Stein (2012)	Stein EA et al. Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial.	Lancet 2012; 380(9836): 29–36.
Teramoto (2016)	Teramoto T et al. Efficacy and safety of alirocumab in Japanese subjects (Phase 1 and 2 studies)	Am J Cardiol 2016; 118: 56–63.

Source: Table 2.2-1 (p 31-38) of the resubmission; Table 2.2-2 (p 40-45) of the resubmission
 Note: Abstracts of studies with full publications are not presented

6.7 The key features of the FOURIER trial are summarised in the table below.

Table 5: Key features of the included evidence

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

Source: Table 2.2-1 (p 31-38), Table 2.3-1 (p 47), Table 2.4-1 (p 48) of the resubmission
 Abbreviations: DB, double blind; LDL, low density lipoprotein cholesterol; MC, multi-centre; PC, placebo-controlled; R, randomised.

6.8 The resubmission claimed that the baseline risk of cardiovascular events in the FOURIER trial may not be generalisable to the requested PBS populations as participants in cardiovascular outcome trials typically have a lower cardiovascular risk compared to real-world populations. The resubmission also claimed that trial participants would have a lower overall cardiovascular risk due to the lower LDL threshold for treatment eligibility (1.8 vs. 2.6 mmol/L) and no requirement regarding prior ezetimibe treatment compared to the PBS population. The ESC advised that it would be reasonable to assume the high-risk subgroups identified in the PBS restriction would have a higher baseline cardiovascular risk than the ITT population in FOURIER.

6.9 It was unclear whether the FOURIER high-risk subgroups had a higher or lower baseline risk compared to the nominated PBS populations due to differences in the definitions of high-risk features, baseline LDL levels and prior therapy requirements. The PSCR claimed that FOURIER, consistent with CTTC and CTTC 2012, shows that reduction in LDL-c is consistent, regardless of baseline risk, and considered there to be no plausible reason that the results seen in the FOURIER high-risk subgroups would not be generalisable to the proposed PBS restriction. The ESC also considered there was consistency in the lipid-lowering trial results from FOURIER, CTTC and ODYSSEY, and advised that the benefit of LDL-c lowering with evolocumab had been clearly established.

6.10 Additionally, the resubmission did not report the proportion of patients in the FOURIER trial who had at least one high-risk feature as defined in the proposed PBS restriction. Based on the available patient characteristics it can be deduced that high-risk patients (as defined by the resubmission’s proposed restriction) represented at least 60% of the FOURIER population, but this estimate could be substantially higher. Overall, the combined patient population identified by the nominated subgroups may not be substantially different from the overall FOURIER trial population.

Comparative effectiveness

6.11 Key cardiovascular outcomes reported in the FOURIER trial are summarised in the table below.

Table 6: Key cardiovascular time to event analyses reported in the FOURIER trial

Outcome	Evolocumab N = 13,784	Placebo N = 13,780	Hazard ratio (95% CI)
Composite outcomes (first event only)			
Time to cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina, or coronary revascularisation [primary outcome]	1,344 (9.75%)	1,563 (11.34%)	0.85 (0.79, 0.92)
Time to cardiovascular death, myocardial infarction, or stroke [key secondary outcome]	816 (5.92%)	1,013 (7.35%)	0.80 (0.73, 0.88)
CTTC composite (coronary death, myocardial infarction, stroke or coronary revascularisation) [post-hoc outcome]	1,271 (9.22%)	1,512 (10.97%)	0.83 (0.77, 0.90)
Individual outcomes			
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%)	0.73 (0.65, 0.82)
Time to first stroke	207 (1.50%)	262 (1.90%)	0.79 (0.66, 0.95)
- Ischaemic stroke	171 (1.24%)	226 (1.64%)	0.75 (0.62, 0.92)
- 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%)	0.78 (0.71, 0.86)
Time to first hospitalisation for unstable angina	236 (1.71%)	239 (1.73%)	0.99 (0.82, 1.18)

Abbreviations: CTTC, Cholesterol Treatment Trialists’ Collaboration

Source: Table 2.5-1 (p 51) of the resubmission; Table 10-9 (p 138), Table 14-4.3.25 (p 342), Table 14-4.3.26 (p 343) of the FOURIER trial report; Table 2 (p 6) of the Sabatine (2017) publication

6.12 Treatment with evolocumab was associated with a statistically significant decreased risk of cardiovascular events compared to placebo (HR 0.85; 95% CI 0.79, 0.92). Disaggregated cardiovascular outcomes indicate that treatment with evolocumab was associated with a decreased risk of myocardial infarction (HR 0.73; 95% CI 0.65, 0.82), coronary revascularisation (HR 0.78; 95% CI 0.71, 0.86) and ischaemic stroke (HR 0.75; 95% CI 0.62, 0.92) compared to placebo. There was no apparent difference in angina, coronary death, cardiovascular death or all-cause mortality between treatment arms. The ESC considered that, while there was no direct data from the FOURIER trial to

support the length of the time lag or the magnitude of any reduction in cardiovascular mortality, the weight of evidence for the benefit of LDL-c lowering on cardiovascular mortality supports the contention that evolocumab would likely be associated with a reduction in cardiovascular mortality, particularly coronary heart disease mortality, over an appropriate time period. However, the ESC considered that modelling a mortality benefit remained problematic.

- 6.13 A landmark analysis of FOURIER outcomes indicated that relative reductions in myocardial infarction, stroke and coronary revascularisations with evolocumab treatment were generally smaller in the first year compared to later years. There was no apparent difference in angina or mortality between treatment arms in the first year or subsequent years. The resubmission claimed that this analysis indicates that there is a treatment lag between the initiation of evolocumab therapy and the accrual of cardiovascular benefits and that this is consistent with the mechanism of action of evolocumab on occlusive cardiovascular disease.
- 6.14 Subgroup analyses of patient demographics suggested that population/health system effects may be contributing to the differences in cardiovascular outcomes between treatments (e.g. time to cardiovascular death, myocardial infarction, or stroke reported in the FOURIER trial: Europe HR 0.90, 95% CI 0.80, 1.01; North America HR 0.62, 95% CI 0.51, 0.76). Any potential effect of the Australian population/health system on outcomes in a high-risk FOURIER-like population is unknown.
- 6.15 The results of pre-specified and post-hoc subgroup analyses of the key secondary outcome for high-risk cardiovascular populations of the FOURIER trial are summarised in the table below.

Table 7: Key secondary composite endpoint (composite of cardiovascular death, myocardial infarction, or stroke) reported in the FOURIER trial and high-risk subgroups

Population	Evolocumab			Placebo			Hazard ratio (95% CI)	p interaction
	Patients	Event incidence	KM event rate ^a	Patients	Event incidence	KM event rate ^a		
ITT N = 27,564	13,784	816	7.9%	13,780	1,013	9.9%	0.80 (0.73, 0.88)	-
MI subgroup N = 22,351	NR	NR	8.0%	NR	NR	9.9%	0.82 (0.74, 0.91)	NR ^b
No MI subgroup N = 5,213	2,639	130	7.7%	2,574	181	10.2%	0.69 (0.55, 0.87)	
MI subgroup with recent event < 1 years N = 5,711	2,821	182	7.7%	2,890	248	10.9%	0.75 (0.62, 0.91)	NR ^b
MI subgroup without recent event (1 year)	NR	NR	NR	NR	NR	NR	NR	
MI subgroup with recent event < 2 years N = 8,402	4,109	265	7.9%	4,293	362	10.8%	0.76 (0.64, 0.89)	0.18

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Population	Evolocumab			Placebo			Hazard ratio (95% CI)	p interaction
	Patients	Event incidence	KM event rate ^a	Patients	Event incidence	KM event rate ^a		
MI subgroup without recent event (2 year) N = 13,918	7,020	419	8.3%	6,898	470	9.3%	0.87 (0.76, 0.99)	
MI subgroup with multiple events N = 5,285	2,657	NR	12.4%	2,628	320	15.0%	0.79 (0.67, 0.94)	0.57
MI subgroup without multiple events N = 17,047	8,477	NR	6.6%	8,570	512	8.2%	0.84 (0.74, 0.96)	
MI subgroup with multivessel disease N = 5,618	2,812	NR	9.2%	2,806	272	12.6%	0.70 (0.58, 0.84)	0.03
MI subgroup without multivessel disease N = 16,715	8,325	NR	7.6%	8,390	556	8.9%	0.89 (0.79, 1.00)	
MI subgroup with any high-risk factor ^c N = 13,973	NR	NR	8.6%	NR	NR	11.0%	0.78 (0.69, 0.88)	0.11
MI subgroup without any high-risk factor ^c N = 8,343	NR	NR	7.3%	NR	NR	7.8%	0.94 (0.78, 1.13)	
Diabetes Subgroup ^d N = 11,031	5,515	417	10.2%	5,516	508	12.2%	0.82 (0.72, 0.93)	0.65
No diabetes subgroup ^d N = 16,533	8,269	399	6.4%	8,264	505	8.4%	0.78 (0.69, 0.89)	
Symptomatic PAD subgroup N = 3,642	1,858	152	13.0%	1,784	195	15.2%	0.73 (0.59, 0.91)	0.41
No symptomatic PAD subgroup N = 23,922	11,926	664	7.2%	11,996	818	9.2%	0.81 (0.73, 0.90)	
Polyvascular disease subgroup N = 3,563	NR	NR	16.0%	NR	NR	16.7%	0.86 (0.71, 1.04)	NR ^e
No polyvascular disease subgroup	NR	NR	NR	NR	NR	NR	NR	
Low risk TIMI (1 point) N = 1,524	NR	NR	3.8%	NR	NR	5.0%	0.73 (0.43, 1.23)	0.94

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Population	Evolocumab			Placebo			Hazard ratio (95% CI)	p interaction
	Patients	Event incidence	KM event rate ^a	Patients	Event incidence	KM event rate ^a		
Intermediate risk TIMI (2-4 points) N = 21,726	NR	NR	6.7%	NR	NR	8.6%	0.79 (0.71, 0.89)	
High-risk TIMI (≥ 5 points) N = 4,314	NR	NR	15.5%	NR	NR	19.1%	0.80 (0.67, 0.95)	

Source: Table 2.6-1 (p 60) of the resubmission; Table 14-4.6.23 (p 380), Table 14-4.6.24 (p 381-382) of the FOURIER trial report; Bohula et al (2017) TIMI publication; Bonaca et al (2018) PAD publication; Sabatine et al (2017) main publication; Sabatine et al (2018) severe CAD publication; Sabatine et al (2017) diabetes publication

Abbreviations: MI, myocardial infarction; NR, not reported; PAD, peripheral arterial disease

^a Based on three year Kaplan-Meier estimates

^b The FOURIER trial did not assess subgroups defined as prior MI or no prior MI or subgroups defined by recent MI within 1 year or beyond 1 year. Instead, subgroup analyses were based on the history of MI (no prior MI, prior MI within 1 year, prior MI in previous 1-2 years, prior MI > 2 years ago). The p-interaction term by history of MI was 0.29

^c Any high risk factor included patients with multiple MI events, patients with recent MI events and patients with multivessel disease

^d Based on patient history or review of baseline clinical data

^e The FOURIER trial did not assess subgroups defined as polyvascular disease or no polyvascular disease. Instead, subgroup analyses were based on type of atherosclerotic disease; MI alone, stroke alone, PAD alone or polyvascular disease. The p-interaction term by type of disease was 0.38

Note: Shaded rows indicate values used to inform the economic analysis.

- 6.16 Patients with high-risk TIMI scores (≥ 5 points on the modified 10-point scale), patients with symptomatic peripheral arterial disease/polyvascular disease and patients with multiple myocardial infarctions had the highest event rates for the key secondary outcome. The apparent high baseline risk in the symptomatic PAD population should be interpreted with caution given that this risk is at least partially attributable to a substantial proportion of these patients having polyvascular disease (2.5 year Kaplan-Meier event rate in the placebo arm for PAD only patients 10.3% vs. 13.0% in all PAD patients).
- 6.17 The relative treatment effects associated with evolocumab were similar across most cardiovascular subgroups with the exception of patients with and without multivessel disease (p interaction: 0.03). Subgroup results for the polyvascular disease population are difficult to interpret although it may be reasonable to assume that the treatment effect from the overall trial population also applies to this subgroup (p interaction by disease subtype: 0.38).
- 6.18 The distribution of cardiovascular events appeared to vary between populations with myocardial infarction subgroups having a higher risk of myocardial infarction while diabetes and PAD subgroups had a higher risk of stroke events and cardiovascular death.

Comparative harms

- 6.19 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.

- 6.20 In regards to adverse events of special interest, treatment with evolocumab was associated with a higher incidence of mild to moderate hypersensitivity reactions and injection site reactions.
- 6.21 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.
- 6.22 No new safety concerns were identified in the most recent Periodic Safety Update Report (PSUR) for evolocumab covering the period from January 2018 to July 2017

Benefits/harms

- 6.23 On the basis of direct evidence presented in the resubmission, for every 1,000 hypercholesterolemia patients with atherosclerotic disease and additional risk factors who are treated with evolocumab in comparison to placebo would result in:
- Approximately a 60% relative reduction in LDL levels.
 - 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.
- 6.24 On the basis of subgroup analyses of high-risk cardiovascular populations in the FOURIER trial, the number needed to treat with evolocumab versus placebo is likely to be smaller for individual high-risk populations (multiple events, polyvascular disease, multivessel disease, recent event, peripheral arterial disease, diabetes, high-risk TIMI ≥ 5 points on the modified 10 point scale) due to apparent differences in baseline cardiovascular risk (see Table 7). For every 1,000 patients treated with evolocumab in comparison to placebo over a mean duration of 2 years (based on crude estimates calculated by applying the hazard ratio from the ITT population to the Kaplan-Meier event rates reported in the placebo arm of each subgroup)

- Approximately 22 fewer patients with an MI in the previous year would experience a cardiovascular death, MI or stroke.
- Approximately 30 fewer patients with previous multiple MI events would experience a cardiovascular death, MI or stroke.
- Approximately 34 fewer patients with a previous MI and multivessel disease would experience a cardiovascular death, MI or stroke (calculated using observed incidence as previous MI and multivessel disease was a potential treatment effect modifier).
- Approximately 24 fewer patients with diabetes would experience a cardiovascular death, MI or stroke.
- Approximately 30 fewer patients with symptomatic peripheral arterial disease would experience a cardiovascular death, MI or stroke.
- Approximately 33 fewer patients with polyvascular disease would experience a cardiovascular death, MI or stroke.
- Approximately 38 fewer patients with high-risk TIMI scores (≥ 5 points) would experience a cardiovascular death, MI or stroke.

Clinical claim

- 6.25 The resubmission described evolocumab as superior in terms of efficacy and similar in terms of safety compared to placebo. The ESC considered this claim was reasonable.
- 6.26 The PBAC considered that the claim of superior comparative effectiveness versus placebo was reasonable.
- 6.27 The PBAC considered that the claim of similar comparative safety compared to placebo was reasonable.

Economic analysis

- 6.28 The resubmission presented a stepped economic evaluation of evolocumab for the treatment of non-FH patients with atherosclerotic disease and additional risk factors as an add-on to existing therapies. 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. The ESC noted that CV events were modelled by applying LDL treatment effects to a composite cardiovascular event rate and distributing these events across subtypes (myocardial infarction, ischaemic stroke, coronary death). The ESC considered this was not robust due to differences in components of the composite event rate between sources, and treatment effects by event type. The ESC reiterated its previous advice that a trial-based economic evaluation (and model) using cardiovascular outcomes (individual

event estimates) would have been more appropriate. The ESC also noted that the statin intolerant population was not incorporated into the model.

- 6.29 The resubmission did not present an economic analysis to support the proposed expansion of the current PBS listing of evolocumab for the treatment of FH to include patients with atherosclerotic disease who have an LDL level between 2.6 and 3.3 mmol/L despite optimised treatment with statins and ezetimibe (refer to Paragraph 6.40 and 7.13).
- 6.30 Key changes to the economic model (resubmission model versus previous submission) included changes to the modelled population (atherosclerotic disease with LDL > 3.3 mmol/L vs. atherosclerotic disease with additional risk factors with LDL > 2.6 mmol/L), mortality lag (3.6 years vs. 2 years with linear increase to maximum effect over next 2 years), baseline cardiovascular risk (0.05 vs. 0.085 events per subject year), risk multipliers (multiplier for age increased 1.03 vs 1.06; new multiplier for subsequent events), distribution of cardiovascular events (MI 37.8%; IS 27.7%; CV death 34.5% vs. MI: 34.0%; IS: 23.5%; CV death: 42.4%) and a correction to the calculation of acute myocardial infarction QALY decrement.

Table 8: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-effectiveness analysis/cost-utility analysis
Outcomes	% reduction in LDL; life years; quality-adjusted life years
Time horizon	35 years (25 years in pre-PBAC response revised base case)
Methods used to generate results	Markov cohort expected value analysis (with half-cycle correction)
Treatments	Evolocumab, placebo
Health states	Five health states: baseline health state (atherosclerotic disease), myocardial infarction (with no history of stroke), ischaemic stroke (with or without a history of myocardial infarction), cardiovascular death and non-cardiovascular death
Cycle length	Monthly
Transition probability	Transition probabilities were derived from the baseline composite cardiovascular event rate adjusted for LDL treatment effects converted to relative reductions in cardiovascular event rates. Estimates were adjusted for the one-month cycle length and transformed into probabilities. Probabilities were allocated to individual events based on the probability that an event is fatal and the probability that a non-fatal event is an MI or IS. The probability of a cardiovascular event was adjusted by time in model and the occurrence of a prior modelled event. The probability of a cardiovascular event being fatal were adjusted by time in model
Discount rate	5% for costs and outcomes
Software package	Excel 2010

Source: Table 3.1-1 (p 76) of the resubmission

Abbreviations: CHD, coronary heart disease; IS, ischaemic stroke; LDL, low density lipoprotein cholesterol; MI, myocardial infarction

- 6.31 All patients start in the baseline health state with atherosclerotic disease. In any month, patients can have no event or experience a non-fatal myocardial infarction, non-fatal ischaemic stroke, cardiovascular death, or non-cardiovascular death. Patients experiencing multiple non-fatal events accrue the acute costs and consequences of each event and have ongoing chronic costs and consequences based on the most severe event. The model allows patients on active treatment to

discontinue therapy with no further drug costs and the same transition probabilities as placebo.

6.32 Key drivers of the economic model are summarised in the table below

Table 9: Key drivers of the model

Description	Method/Value	Impact
Time horizon	<p>The economic model was based on a 35-year time horizon.</p> <p>The PBAC has previously suggested that a 25-year time horizon may also be informative given the average patient age of the target population (64 years in previous models; 68 years in current model). The ESC reiterated that 25 years would have been informative. The pre-PBAC response revised base case used a 25-year time horizon.</p>	<p>High for short time horizons (< 15 years), favours evolocumab</p>
Baseline risk	<p>Baseline cardiovascular risk based on Swedish Registry data (Lindh 2019) with additional risk adjustments for high-risk groups calculated from the FOURIER trial.</p> <p>The resubmission argued that the baseline risk in the FOURIER trial population should not be used to inform the model as cardiovascular trials typically include lower risk patients than real world populations. Additionally, the resubmission claimed that trial participants would have a lower overall cardiovascular risk compared to the PBS population due to the lower LDL threshold for treatment eligibility (1.8 vs. 2.6 mmol/L) and no requirement regarding prior ezetimibe treatment. The average baseline LDL in FOURIER was 2.5 mmol/L. The resubmission assumed that based on the qualifying threshold of 2.6 mmol/L that PBS patients would have an average LDL of approximately 3.3 mmol/L.</p> <p>The ESC considered that the patient population identified in the Lindh study is unlikely to be representative of the requested PBS populations (patients receiving optimised treatment with statins and ezetimibe) given the very low levels of high intensity statin use. Additionally, the Lindh study did not assess ongoing use of statin therapy during follow-up (the study authors noted that patients may have discontinued their therapy several years before experiencing an event) and therefore results may not be representative of an actively treated population. Also, the patient population in the Lindh study was older than the modelled patient population (72.5 vs. 68 years). Given that the resubmission has noted that baseline risk increases with age it was inappropriate to apply these risks to the modelled population at baseline. The ESC advised that Lindh likely overestimates the true baseline risk with respect to the proposed PBS population (see Table 2 in the Background section).</p> <p>Overall, the ESC considered it was inappropriate to apply FOURIER risk adjustments to estimates from the Lindh study as this assumes a similar distribution of cardiovascular risk factors between studies (which is not consistent with the available data). To address this, the pre-PBAC response revised base case used CV event rates from FOURIER adjusted for the proposed high-risk subgroups and a higher baseline LDL-C in the PBS population.</p>	<p>High, favours evolocumab</p>
Distribution of cardiovascular events	<p>The resubmission estimated the distribution of cardiovascular events (myocardial infarction: 34.0%; ischaemic stroke 23.5%; cardiovascular death 42.4%) based on a sponsor-commissioned analysis of Swedish registry data (Lindh, 2019).</p> <p>The Swedish registry data identified an older, under-treated population with a relatively high prevalence of stroke (and hypertension) and lower levels of intensive statin treatment with unknown adherence to hypolipidaemic treatments. In contrast, the FOURIER trial provides data on generally well-managed patients who are actively being treated with moderate-to-high intensity statins (with or without ezetimibe). The most closely comparable distribution of events reported in the FOURIER trial was for the</p>	<p>Moderate, favours evolocumab</p>

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Description	Method/Value	Impact
	<p>placebo arm ITT population: myocardial infarction: 58.7%, stroke: 22.4%, cardiovascular death 18.9% (FOURIER all event analysis).</p> <p>The PSCR claimed that use of risk directly from the FOURIER clinical trial would serve to underestimate risk in clinical practice, as real-world event rates have been consistently higher than in RCTs. The ESC agreed with the PSCR that baseline risk in the FOURIER trial may be lower than the proposed PBS population. However, the ESC noted that use of Lindh to inform baseline cardiovascular risk estimates and the distribution of cardiac events resulted in a larger modelled treatment benefit (change in LDL) than FOURIER, and a much larger modelled reduction in coronary death. The ESC considered that use of 'real world data' would have been more reasonable if it had appropriately captured the proposed PBS population.</p> <p>To address this, the pre-PBAC response revised base case used the distribution of CV events reported in the placebo arm ITT population of the FOURIER trial (i.e. myocardial infarction: 58.7%, stroke: 22.4%, cardiovascular death 18.9%). As noted above, the pre-PBAC response also used the event rate from FOURIER adjusted for the proposed high risk subgroups and a higher baseline LDL-c in the PBS population (i.e. the pre-PBAC response used a CHD event rate for untreated patients of 7.1% per year in Year 1 based on an LDL-c difference between the PBS population of FOURIER trial population of 0.93 mmol/L and a HR of 1.35 to account for the higher risk subgroups).</p>	
Treatment compliance	<p>The resubmission estimated treatment adherence for evolocumab based on the proportion of patients discontinuing treatment in the FOURIER trial. The resubmission assumed evolocumab would have perfect persistence.</p> <p>The Commentary considered the approach used to estimate adherence rates in the economic model was inappropriate as discontinuation rates are a measure of persistence rather than adherence.</p> <p>The economic model implemented the adherence estimates as a flat reduction in drug costs. This was not appropriate as non-adherence would affect both costs and health outcomes. The ESC agreed with the Commentary that an assumption of 100% persistence was inappropriate.</p> <p>The available clinical data does not support the assumption of perfect persistence. Based on the FOURIER trial approximately 12.4% of patients discontinued treatment over a mean duration of 2.2 years. There are limited available data on treatment persistence to PCSK9 inhibitors outside of clinical trials.</p> <p>To address this, the pre-PBAC response revised base case applied an assumption that 1% of patients discontinue treatment each monthly cycle for the first 4 years.</p>	High, favours evolocumab

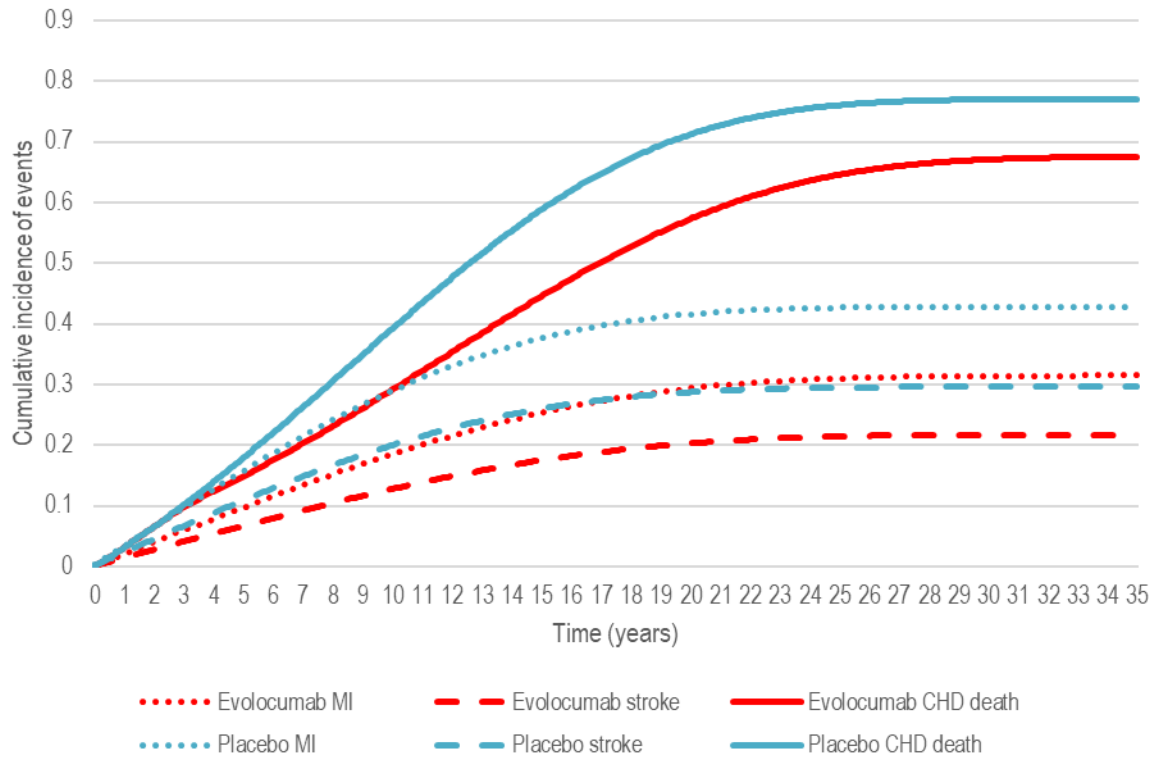
Source: Constructed during the evaluation

6.33 The resubmission estimated an increased risk of cardiovascular events with time, an increased risk of cardiovascular death with time and the increased risk of subsequent events based on sponsor-commissioned analysis of the UK Clinical Practice Research Datalink GOLD database (retrospective, longitudinal, observational dataset with linked electronic medical records, hospital episode data and mortality data). The source data were poorly documented in the resubmission. The evaluation and the ESC considered that the resubmission did not adequately justify the use of different cohorts and methodologies to estimate the different risk multipliers. While the

available data supports the use of risk multipliers, the magnitude of the adjustments remains uncertain due to the limitations of the current evidence.

- 6.34 The resubmission revised the estimate of mortality lag from 3.6 years used in the previous submission to a 2-year lag with a linear progression to maximum treatment effect over the next 2 years. The resubmission argued that the revised mortality lag approach corresponds to the observed lag in treatment effect on cardiovascular mortality in the statin and alirocumab studies and also corresponds more directly to the likely mechanism of plaque stabilisation and reduction increasing over time than the previous 'all-or-nothing' approach. The Commentary and the ESC considered that the appropriate method to model a time lag in cardiovascular death remains unclear. The ESC noted that the PBAC had previously indicated a preference for a lag of 3.6 years and considered this to be reasonable. To address this, the pre-PBAC response revised base case applied a 3.6 year mortality lag (per the previous submission).
- 6.35 The resubmission claimed that the average LDL of a population could be inferred from the LDL threshold used to define the population. The resubmission attempted to quantify this relationship based on a post-hoc analysis of individual patient data from the placebo arm of the FOURIER trial comparing mean baseline LDL levels in populations defined by different LDL thresholds. Based on the proposed LDL qualifying criterion of 2.6 mmol/L in the target PBS population, the resubmission claimed that patients would have an average LDL of approximately 3.3 mmol/L. The Commentary and the ESC considered that it was difficult to assess the generalisability of the analysis as there are major differences between the trial population and the proposed PBS population as well as additional uncertainty regarding whether a subsidised threshold for treatment would change the distribution of patients.
- 6.36 The cumulative incidence of cardiovascular events over the course of the resubmission model is presented in the figure below.

Figure 1: Cumulative incidence of myocardial infarction, stroke and CHD death (resubmission model)



Source: constructed during the evaluation using Evolocumab_Economic_Model Excel model provided with the resubmission
 Abbreviations: CHD, coronary heart disease; MI, myocardial infarction

- 6.37 The cumulative incidence curves show that the predominant cardiovascular event in the model was CHD death, which is a major driver of the economic model.
- 6.38 The results of the modelled economic evaluation are summarised below. The presented results were based on an additional stepped economic analysis that was conducted during the evaluation to demonstrate the impact of changes to the economic model between the previous July 2018 submission and the current resubmission. The results presented below are based on the model submitted in the resubmission.

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Table 10: Results of the stepped economic evaluation from previous submission to resubmission model

Step and component	Evolocumab	Placebo	Increment
Step 1: Variables from the July 2018 evolocumab submission (demographics, baseline risk, LDL level, risk multipliers, mortality lag, cardiovascular event distribution, utility values) in the July 2018 economic model			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	8.942	7.886	1.056
Incremental cost per QALY gained			\$ [REDACTED]
Step 2: Variables from the July 2018 evolocumab submission in the July 2019 economic model with minor adjustments			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	8.941	7.883	1.057
Incremental cost per QALY gained			\$ [REDACTED]
Step 3: Updated baseline LDL levels (5.0 to 3.3 mmol/L)			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	8.577	7.883	0.693
Incremental cost per QALY gained			\$ [REDACTED]
Step 4: Updated demographics (baseline age 64 to 68 years; female 30% to 38%)			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	8.103	7.508	0.595
Incremental cost per QALY gained			\$ [REDACTED]
Step 5: Updated utility values (acute MI QALY decrement -0.3096 to -0.0258)			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	8.141	7.565	0.575
Incremental cost per QALY gained			\$ [REDACTED]
Step 6: Updated baseline risk (0.05 to 0.085 events per subject year)			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	7.236	6.532	0.704
Incremental cost per QALY gained			\$ [REDACTED]
Step 7: Updated risk multipliers (age multiplier 1.03 to 1.06; prior event multiplier 1.00 to 1.17)			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	6.752	5.997	0.755
Incremental cost per QALY gained			\$ [REDACTED]
Step 8: Updated mortality lag (3.6 year lag to 2 year lag with a linear progression to maximum treatment effect over the next 2 years)			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	6.791	5.997	0.795
Incremental cost per QALY gained			\$ [REDACTED]
Step 9: Updated cardiovascular event distribution (MI: 37.8%; IS: 27.7%; CV death: 34.5% to MI: 34.0%; IS: 23.5%; CV death: 42.4%)			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	6.596	5.806	0.790
Incremental cost per QALY gained			\$ [REDACTED]

Source: 'Evolocumab Model v5.09a' Excel spreadsheet; 'Evolocumab_Economic_Model' Excel spreadsheet

Abbreviations: CV, cardiovascular; IS, ischaemic stroke; MI, myocardial infarction; QALY, quality adjusted life year

6.39 Based on the economic model submitted in the resubmission, treatment with evolocumab was associated with a cost per QALY gained of \$15,000 - \$45,000 compared to placebo (add-on to existing therapies) in non-FH patients with atherosclerotic disease and additional cardiovascular risk factors. The resubmission did not provide economic analyses for the individual high-risk subgroup populations. Limited economic analyses for these populations were conducted during the evaluation.

- 6.40 The cost effectiveness of evolocumab versus placebo for the treatment of FH patients with atherosclerotic disease who have an LDL level between 2.6 and 3.3 mmol/L despite optimised treatment with statins and ezetimibe was also estimated during the evaluation. Two approaches were used; by applying the resubmission's proposed price and LDL range to the previous FH model as well as importing the patient characteristics from the previous model (with the exception of LDL range) into the resubmission model. These analyses suggested that (at the price proposed in the resubmission) treatment with evolocumab was associated with a cost per QALY gained of between \$15,000 - \$45,000 compared to placebo (add-on to existing therapies) in FH patients with atherosclerotic disease who have an LDL level between 2.6 and 3.3 mmol/L (the March 2018 submission previously estimated a cost per QALY gained of \$15,000 - \$45,000 in patients with an LDL > 3.3 mmol/L). The PSCR claimed that lowering the qualifying threshold for the FH ASCVD population will align with the proposed non-FH threshold, and considered this to be appropriate as the baseline CV risk in the FH ASCVD population is at least as high for the proposed non-FH subgroups. The ESC considered that if the cost-effectiveness of the non-FH population is accepted, extending the eligible population for FH to include an LDL-c level of 2.6 mmol/L would still only be cost-effective if the baseline risk is at least as high (or higher) than that for the non-FH population, and if at the same price as accepted for non-FH. The PBAC considered that patients with FH who have symptomatic ASCVD and LDL-c levels over 2.6 mmol/L would likely have at least an equivalent lifetime risk as the non-FH population (with additional risk factors) identified in the revised restriction.
- 6.41 The results of key sensitivity analyses (based on the resubmission model) are summarised below.

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Table 11: Results of key sensitivity analyses (based on resubmission model)

Analyses	Incremental cost	Incremental QALY	ICER
Base case of resubmission model	\$ [REDACTED]	0.790	\$ [REDACTED]
Time horizon (base case 35 years)			
15 years	\$ [REDACTED]	0.519	\$ [REDACTED]
25 years	\$ [REDACTED]	0.771	\$ [REDACTED]
Baseline LDL-cholesterol (base case 3.3 mmol/L)			
2.60 (qualifying threshold for PBS population)	\$ [REDACTED]	0.629	\$ [REDACTED]
Annual cardiovascular event rate (base case 0.085)			
0.042 (based on the FOURIER trial)	\$ [REDACTED]	0.659	\$ [REDACTED]
Annual cardiovascular event rate increase (base case 1.06)			
1.00 (no multiplier)	\$ [REDACTED]	0.751	\$ [REDACTED]
1.03 (based on previous REACH registry estimate)	\$ [REDACTED]	0.794	\$ [REDACTED]
Subsequent event risk multiplier (base case 1.17)			
1.00 (no multiplier)	\$ [REDACTED]	0.755	\$ [REDACTED]
Annual case fatality rate increase (base case 1.07)			
1.00 (no multiplier)	\$ [REDACTED]	0.793	\$ [REDACTED]
Event distribution (base case: MI 34.0%, IS 23.5%, CHD death 42.4%)			
FOURIER first event distribution (MI 62.0%; IS 23.5%; CHD death 14.5%)	\$ [REDACTED]	0.731	\$ [REDACTED]
FOURIER all event distribution (MI 58.7%; IS 22.4%; CHD death 18.9%)	\$ [REDACTED]	0.753	\$ [REDACTED]
Previous distribution from Heart Protection study (MI 37.8%; IS 27.7%; CHD death 34.5%)	\$ [REDACTED]	0.795	\$ [REDACTED]
Cardiovascular mortality benefit time lag (base case 2 years with a linear improvement to maximum treatment effect over the next 2 years)			
No mortality lag	\$ [REDACTED]	1.016	\$ [REDACTED]
3.6 year lag (based on previous model)	\$ [REDACTED]	0.745	\$ [REDACTED]
5 year lag (consistent with sponsor-commissioned Fonarow 2017 model)	\$ [REDACTED]	0.649	\$ [REDACTED]
Persistence (base case no discontinuations)			
1% discontinuations per month for duration of model	\$ [REDACTED]	0.311	\$ [REDACTED]
2% discontinuations per month for duration of model	\$ [REDACTED]	0.158	\$ [REDACTED]
1% discontinuations per month for 4 years	\$ [REDACTED]	0.497	\$ [REDACTED]
2% discontinuations per month for 4 years	\$ [REDACTED]	0.316	\$ [REDACTED]

Source: Table 3.9-1 (p 116-118), Table 3.9-2 (p 119) of the resubmission

Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year

The redacted table shows ICERs in the range of \$15,000/QALY - \$75,000/QALY.

- 6.42 The results of the sensitivity analyses indicated that the resubmission’s model was most sensitive to time horizon, treatment persistence, baseline risk and mean LDL level.
- 6.43 During the evaluation, scenario analyses were conducted for each of the high-risk populations specified in the restriction, using patient demographics, baseline risk and event distributions directly from the FOURIER trial. These analyses were limited to a 25 year time horizon and incorporated a 1% discontinuation rate per month for four years. However, the PSCR claimed that the analyses conducted during the evaluation neglected to correct for, at a minimum, baseline LDL-c being around 1 mmol/L lower in FOURIER than expected for the proposed PBS population.

- 6.44 The ESC considered the PSCR correctly highlighted the need to adjust the baseline risk of the FOURIER trial. However, the ESC considered that the PSCR approach was a crude method for adjusting baseline risk as inverting the reduction in risk due to treatment effects may not accurately represent increases in risk due to different patient populations (populations that achieve lower LDLs with statins may be inherently different to populations who do not achieve these targets, e.g. due to lack of compliance etc). Additionally, the LDL adjustment proposed in the PSCR was based on a 1.0 mmol/L difference between the trial population and the proposed PBS populations, which was inconsistent with the submission, which suggested a 0.8 mmol/L difference between populations. Therefore, this alternative value (0.8 mmol/L) was used as the LDL adjustment in further sensitivity analyses conducted by the ESC.
- 6.45 The ESC considered that the results of these scenario analyses were subject to substantial uncertainty due to differences in the definitions of high risk factors between the economic analyses and the proposed PBS restriction. For example, the baseline risk for the multiple event population in the economic model was based on patients with a history of multiple myocardial infarctions and may not represent the baseline risk of patients with other combinations of multiple events such as:
- Myocardial infarction and revascularisation procedure;
 - Unstable angina hospitalisation and revascularisation procedure;
 - Ischaemic stroke and revascularisation procedure;
 - Multiple revascularisation procedures;
 - Multiple unstable angina hospitalisations;
 - Myocardial infarction and ischaemic stroke;
 - Unstable angina hospitalisation and ischaemic stroke; or
 - Multiple ischaemic strokes
- 6.46 Further, there was insufficient data to estimate the cost-effectiveness of evolocumab treatment in ATSI populations or diabetes subgroups consistent with the ezetimibe PBS listing (diabetes and aged 60 years or older; diabetes with microalbuminuria) as proposed by the ESC.
- 6.47 The ESC considered that an additional source of uncertainty in the economic model included the change in mortality lag from a 3.6 year lag to a 2 year lag, and then a linear reduction for a further 2 years, especially given that mortality is the main driver of the economic model. As a consequence of this considerable uncertainty in the economic model, the ESC considered that the proposed ICER in the submission was highly uncertain and this needed to be reflected in a more conservative base case and scenario analyses. The ESC considered that a potential way forward to address some of the considerable economic uncertainty would be a re-specified base case using the current model with the following suggested parameters: a baseline LDL-c adjustment of 0.8 mmol/L, event distribution from the FOURIER trial, and a 25-year time horizon. The PBAC considered that, even with this more conservative base case, the most

appropriate method to model the likely mortality benefits of evolocumab remained unclear and that this was a source of considerable uncertainty in the economic model.

6.48 To address issues raised by the ESC, the pre-PBAC response provided a revised economic model based on:

- a lower price (rebate increased from ██████% to ██████%);
- a 25 year time horizon consistent with the ESC advice (rather than 35 years in the resubmission base case);
- a mortality lag of 3.6 years consistent with the previous submission (rather than a lag of 2 years with linear adjustment for 2 years per the resubmission base case). The resulting modelled mortality gains are outlined in Figure 2 below;
- a treatment discontinuation rate of 1% per cycle for the first 4 years consistent with the ESC advice (rather than no discontinuation per the resubmission base case); and
- the cardiovascular event rate and the distribution of cardiovascular events were based on FOURIER data consistent with the ESC advice (rather than Swedish registry data per the resubmission base case). Cardiovascular event rates were adjusted: for the proposed high risk subgroups (HR of 1.35 applied, unchanged from the resubmission model); and for the difference in baseline LDL-c between FOURIER and the proposed PBS population using an LDL-c difference of 0.93 mmol/L. The pre-PBAC response stated the latter was based on the difference between the mean LDL-c level estimated in the proposed PBS population (3.3 mmol/L for a population with an LDL-c threshold of 2.6 mmol/L) and the observed baseline LDL-c level in FOURIER, which the pre-PBAC response stated to be 2.37 mmol/L. However, the PBAC noted this was the median LDL-c level in FOURIER, rather than the mean level of 2.53 mmol/L. Using the mean LDL-c level in FOURIER would result in an LDL-c difference of 0.8 mmol/L (3.3 minus 2.53 mmol/L).

Figure 2: Proportion of patients who have died in the pre-PBAC response economic model

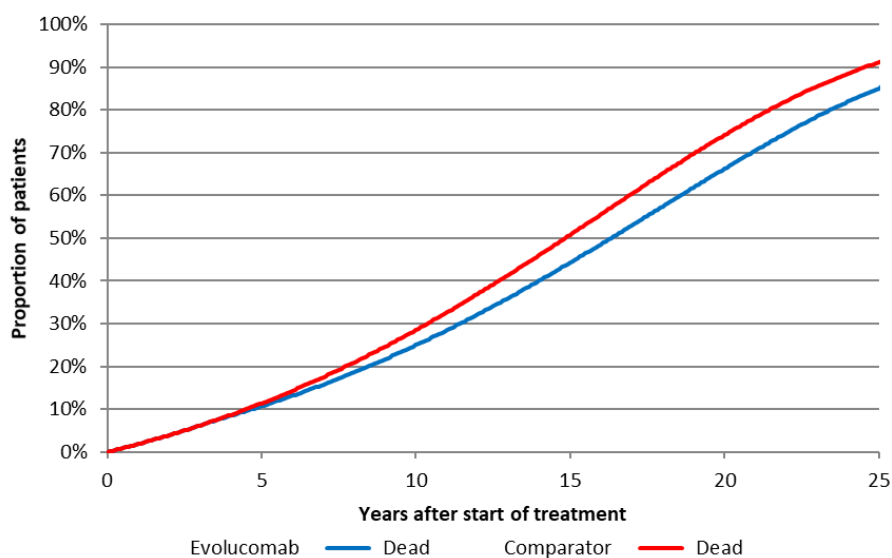


Figure 3: Proportion of patients who have died in the pre-PBAC response economic model

Source: 'Model' worksheet of 'Evolocumab_Economic_Model_190627c.xlsx' submitted with the pre-PBAC response

6.49 The results of the model presented in the pre-PBAC response are outlined in the table below, along with scenario analyses for each of the high-risk populations specified in the restriction. Consistent with advice from the ESC, the pre-PBAC response removed the 'MI subgroup with recent event < 1 year' (i.e. to reflect removal of the PBS criteria 'Patient must have had an acute coronary syndrome (i.e. myocardial infarction or unstable angina) within the previous 12 months'). The table also presents the results for the combined high risk group using an LDL-c adjustment of 0.8 mmol/L (rather than 0.93 mmol/L per the pre-PBAC response).

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Table 12: Pre-PBAC response revised base case and multivariate sensitivity analyses for subgroups^a

		Evolocumab	Placebo	Increment	ICER
Combined high risk ^b	Costs	\$██████	\$██████	\$██████	██████
	QALY	7.931	7.453	0.478	
MI with multiple events ^c	Costs	\$██████	\$██████	\$██████	\$██████
	QALY	7.740	7.252	0.488	
MI with multivessel disease ^d	Costs	\$██████	\$██████	\$██████	\$██████
	QALY	8.085	7.621	0.463	
Diabetes ^e	Costs	\$██████	\$██████	\$██████	\$██████
	QALY	7.867	7.389	0.478	
Symptomatic PAD ^f	Costs	\$██████	\$██████	\$██████	\$██████
	QALY	7.209	6.712	0.497	
PVD ^g	Costs	\$██████	\$██████	\$██████	\$██████
	QALY	7.492	6.969	0.523	
High Risk TIMI ^h	Costs	\$██████	\$██████	\$██████	\$██████
	QALY	6.976	6.479	0.498	
Per pre-PBAC response, but with an LDL-c adjustment of 0.8 mmol/L (rather than 0.93 mmol/L)					
Combined high risk ⁱ	Costs	\$██████	\$██████	\$██████	\$██████
	QALY	7.983	7.511	0.472	

Source: Table 2 of the pre-PBAC response

Abbreviations: ICER = incremental cost-effectiveness ratio; MI = myocardial infarction; PAD = peripheral arterial disease; PVD = peripheral vascular disease; TIMI = Thrombolysis in Myocardial Infarction, QALY = quality adjusted life year

^aAlthough very close, the sponsor could not exactly replicate the ICERs provided in ESC Advice, likely due to rounding.

^b Combined high risk subgroup (multiple MI, MI with multivessel disease, diabetes, symptomatic PAD) (age: default FOURIER, 62.5 years; gender: default FOURIER 24.6% female; baseline risk: 0.042 x 1.35 = 0.057 events per subject year; event distribution: default FOURIER 58.7% MI; 22.4% IS; 18.9% CHD death; time horizon: 25 years; persistence: 1% discontinuations per month for four years; LDL adjustment based on 0.93 mmol/L difference)

^c MI subgroup with multiple MI events (age: 62.2 years; gender: 17.6% female; baseline risk: 0.042 x 1.515 = 0.064 events per subject year; event distribution: 63.3% MI, 17.4% IS, 19.3% CHD death; time horizon: 25 years; persistence: 1% discontinuations per month for four years; LDL adjustment based on 0.93 mmol/L difference)

^d MI subgroup with multivessel disease (age: 61.7 years; gender: 18.8% female; baseline risk: 0.042 x 1.273 = 0.053 events per subject year; event distribution: 63.0% MI, 16.8% IS, 20.3% CHD death; time horizon: 25 years; persistence: 1% discontinuations per month for four years; LDL adjustment based on 0.93 mmol/L difference)

^e Diabetes subgroup (age: 62.6 years; gender: 26.7% female; baseline risk: 0.042 x 1.232 = 0.052 events per subject year; event distribution: 52.9% MI, 24.6% IS, 22.5% CHD death; time horizon: 25 years; persistence: 1% discontinuations per month for four years; LDL adjustment based on 0.93 mmol/L difference).

^f Symptomatic PAD subgroup (age: 64 years; gender: 28.2% female; baseline risk: 0.042 x 1.535 = 0.064 events per subject year; event distribution: 52.3% MI, 22.7% IS, 25.0% CHD death; time horizon: 25 years; persistence: 1% discontinuations per month for four years; LDL adjustment based on 0.93 mmol/L difference)

^g Polyvascular disease subgroup (age: default FOURIER, 62.5 years; gender: default FOURIER 24.6% female; baseline risk: 0.042 x 1.687 = 0.071 events per subject year; event distribution: default FOURIER 58.7% MI; 22.4% IS; 18.9% CHD death; time horizon: 25 years; persistence: 1% discontinuations per month for four years; LDL adjustment based on 0.93 mmol/L difference)

^h High risk TIMI, > 5 points (age: 66 years; gender: 27% female; baseline risk: 0.042 x 1.929 = 0.081 events per subject year; event distribution: default FOURIER 58.7% MI; 22.4% IS; 18.9% CHD death; time horizon: 25 years; persistence: 1% discontinuations per month for four years; LDL adjustment based on 0.93 mmol/L difference)

ⁱ Per table footnote (b) but with LDL adjustment based on 0.8 mmol/L difference.

6.50 The pre-PBAC response revised base case resulted in an ICER of \$15,000/QALY - \$45,000/QALY for the combined high risk group. The PBAC noted this increased to \$15,000/QALY - \$45,000/QALY if an LDL-c adjustment of 0.8 mmol/L was used.

6.51 The ESC noted the cost effectiveness of PCSK9 inhibitors in a modelled Australian population drawing on the FOURIER trial data was assessed in a published paper (Kumar (2018)). As presented in the Commentary, the cost-effectiveness of PCSK9

inhibitors resulted in an ICER over more than \$200,000/QALY when using the FOURIER trial data. The ESC noted several differences between this model and the one presented in the resubmission to account for the substantially different results, including: differences in selected patient populations, model structure, time horizon, circumstances of use, transition probabilities, risk multipliers, cardiovascular mortality lag assumptions, drug costs, disease management costs, death costs and utility values. In particular, no cardiovascular mortality benefit was modelled, there was no adjustment to the baseline risk from the trial, and the cost of evolocumab was approximately 2.5 times higher. The ESC remained concerned about the uncertainty of the ICER in the submission base case and considered that the cost effectiveness of PCSK9 inhibitors in any usage beyond appropriate high-risk subgroups would be unacceptably high at the proposed price.

Drug cost/patient/year

6.52 The drug cost per patient for evolocumab is summarised in the table below. The PBAC noted this was based on the price proposed in the resubmission and that a further price reduction had been proposed in the pre-PBAC response in the form of an increase in the rebate from ██████% to ██████%.

Table 13: Drug cost per patient for evolocumab (based on price proposed in resubmission)

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	Not reported		Not estimated	88% ^a	
Persistence	88% ^b		100% ^c	-	
Adherence	Not reported		88% ^a	-	
Scripts/year	-		██████	██████	██████
Cost/patient/script	-		-	\$██████	\$██████
Cost/patient/month	-		\$██████	-	-
Fortnightly/ monthly dosing split	Not reported		Not estimated	95% ⁱ	5% ⁱ
Cost/patient/year	-		\$██████	\$██████	

^a Assumed based on treatment discontinuations in the FOURIER trial

^b Based on proportion of patients discontinuing treatment in the FOURIER trial

^c Assumed

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

^e Based on assumed compliance rate (88%) and 13.04 scripts per patient per year

^f Based on assumed compliance rate (88%) and 12 scripts per patient per year

^g Effective price based on ██████% rebate on government expenditure proposed in the resubmission

^h Effective price per script: \$630.36 (proposed DPMQ) - \$██████ (estimated rebate) = \$██████. Adjusted to monthly estimate \$██████/28 (script duration in days) x 365.25/12 (days per month)

ⁱ Assumed

^j Based on estimated scripts/year (10.56) and cost/patient/month (\$██████) x 12 months

^k Based on scripts/year for fortnightly dose (11.48) and corresponding cost per script (\$██████); scripts/year for monthly dose (10.56) and corresponding cost per script (\$██████); weighted by assumed fortnightly/monthly dosing split (95% and 5% respectively)

Estimated PBS usage & financial implications

6.53 This resubmission was considered by DUSC.

Non-familial hypercholesterolaemia

6.54 The submission used a mixed market share/epidemiological approach to estimate the eligible patient population with non-familial hypercholesterolaemia and atherosclerotic disease who have additional risk factors and LDL levels above 2.6 mmol/L despite optimised treatment with statins and ezetimibe.

6.55 Key changes to the budget impact estimates, compared with the previous submission, included changes to patient eligibility criteria and a shift in the proposed place in therapy to third-line after statins and ezetimibe.

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Table 14: Estimated utilisation and cost of evolocumab to the PBS/RPBS in the first six years of listing for patients with non-familial hypercholesterolaemia and atherosclerotic disease who have additional risk factors and LDL levels above 2.6 mmol/L des

	Year 1 (2020)	Year 2 (2021)	Year 3 (2022)	Year 4 (2023)	Year 5 (2024)	Year 6 (2025)
Patients using ezetimibe with or without statins	██████	██████	██████	██████	██████	██████
Patients with symptomatic ASCVD	██████	██████	██████	██████	██████	██████
Patients with non-familial disease	██████	██████	██████	██████	██████	██████
- Patients with multiple events (12.58%) ^a	██████	██████	██████	██████	██████	██████
- Patients with multi-vessel disease (9.35%) ^a	██████	██████	██████	██████	██████	██████
- Patients with recent events (9.72%) ^a	██████	██████	██████	██████	██████	██████
- Patients with peripheral arterial disease (10.11%) ^a	██████	██████	██████	██████	██████	██████
- Patients with diabetes (17.47%) ^a	██████	██████	██████	██████	██████	██████
- Patients who are ATSI (0.65%) ^a	██████	██████	██████	██████	██████	██████
Total patients with high risk factors (60% overall) ^b	██████	██████	██████	██████	██████	██████
Total high risk non-FH ASCVD patients with LDL > 2.6 mmol/L despite optimised treatment with statins and ezetimibe ^c	██████	██████	██████	██████	██████	██████
Evolocumab uptake rate	███%	███%	███%	███%	███%	███%
Patients treated with evolocumab	██████	██████	██████	██████	██████	██████
Total evolocumab scripts	██████	██████	██████	██████	██████	██████
Total cost of evolocumab (effective DPMQ)	\$██████	\$██████	\$██████	\$██████	\$██████	\$██████
Patient copayments (\$13.77 per script)	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████
Total cost less copayment	\$██████	\$██████	\$██████	\$██████	\$██████	\$██████

Source: Table 4.2-3 (p 130), Table 4.2-4 (p 130), Table 4.2-5 (p 130), Table 4.2-6 (p 131) of the resubmission; 'Financial Analysis Workbook Final' Excel spreadsheet

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; ATSI, Aboriginal or Torres Strait Islander; DPMQ, dispensed price for maximum quantity; FH, familial hypercholesterolaemia; LDL, low density lipoprotein cholesterol

^a Estimated as mutually exclusive cohorts

^b There was a small discrepancy in patient numbers due to rounding; potentially eligible patients were rounded from 59.885% to 60%. This was amended to 52.8% in the pre-PBAC response revised financial estimates.

The redacted table shows that at year 6, the estimated number of patients was 10,000 – 50,000.

6.56 DUSC considered the estimates for non-familial hypercholesterolaemia presented in the submission to be underestimated. DUSC considered that the main issues were:

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- The multiple steps involved in the estimates with numerous assumptions increases the risk of error.
 - The resubmission estimated the underlying population with symptomatic atherosclerotic disease based on Streamlined Authority coding for ezetimibe. This likely underestimated patient numbers as patients were excluded if their most commonly selected streamlined code was not CHD, PVD or CeVD; however, patients allocated other codes could have symptomatic ASCVD; e.g. diabetes. Further, the analysis of ezetimibe use was based on a 12-month sample period. Thus, DUSC considered the eligible population was underestimated if past use of ezetimibe (beyond 12 months) is used to qualify for treatment.
 - The high-risk groups used to calculate the financial estimates did not match exactly to the groups specified in the requested restriction. The estimation of patients with high-risk features inappropriately excluded a substantial pool of patients who would qualify for treatment under the proposed PBS restrictions.
 - The estimated proportion of patients with LDL levels > 2.6 mmol/L despite treatment with ezetimibe only was substantially different between data sources.
- 6.57 The ESC advised that updated financial estimates would be required to reflect the suggested revisions to the restriction (as outlined in Section 2). The ESC considered that there would be substantial overlap of high-risk subgroups, with potentially some narrowing of the already identified groups and some additional patients in the TIMI risk score ≥ 5 subgroup. To account for uncertainties, the ESC considered the updated estimates should reflect conservative assumptions to reduce the overall risk to Government under a risk share arrangement.
- 6.58 To address this, the pre-PBAC response revised the financial estimates to reflect:
- the price reduction proposed in the pre-PBAC response; and
 - a re-analysis of the FOURIER trial population to determine the proportion of patients who would meet the ESC's revised eligibility criteria. The re-analysis found that 52.8% of patients in FOURIER met the revised eligibility criteria (versus 60% in the resubmission estimates). This revised percentage was applied to determine the percentage of patents with additional risk factors in the pre-PBAC response's revised financial estimates.

Familial hypercholesterolaemia

- 6.59 The resubmission used an epidemiological approach to estimate the eligible patient population with familial hypercholesterolaemia and atherosclerotic disease who have LDL levels between 2.6 and 3.3 mmol/L despite optimised treatment with statins and ezetimibe.

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Table 15: Estimated utilisation and cost of evolocumab to the PBS/RPBS in the first six years of listing for patients with familial hypercholesterolaemia and atherosclerotic disease who have LDL levels between 2.6 and 3.3 mmol/L despite optimised treatment

	Year 1 (2020)	Year 2 (2021)	Year 3 (2022)	Year 4 (2023)	Year 5 (2024)	Year 6 (2025)
Prevalence of FH	73,296	74,508	75,714	76,904	78,080	79,236
FH ASCVD patients with LDL between 2.6 and 3.3 mmol/L	8,063	9,686	10,600	11,536	11,712	11,885
Evolocumab uptake rate	█	█	█	█	█	█
Patients treated with evolocumab	█	█	█	█	█	█
Total evolocumab scripts	█	█	█	█	█	█
Total cost of evolocumab (effective DPMQ)	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Patient co-payments (\$13.77 per script)	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Total cost less co-payment	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

Source: Table 4.2-1 (p 127) of the resubmission; 'Financial Analysis Workbook Final' Excel spreadsheet

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

The redacted table shows that at year 6, the number of patients treated would be less than 10,000.

6.60 DUSC considered the estimates for familial hypercholesterolaemia presented in the submission to be uncertain. The main issues were uncertain: prevalence of disease; diagnosis rates; proportion of patients with LDL between 2.6 and 3.3 mmol/L; uptake rates; and treatment compliance rates.

6.61 The pre-PBAC response revised the financial estimates for the expanded FH population to reflect the further price reduction proposed.

Both populations

6.62 The resubmission's estimate of the total financial implications across all patient populations are summarised in the table below.

Table 16: Estimated budget impact of extending the PBS/RPBS listing of evolocumab to include additional familial hypercholesterolaemia patients and non-familial hypercholesterolaemia patients at very high cardiovascular risk (resubmission estimates)

	Year 1 (2020)	Year 2 (2021)	Year 3 (2022)	Year 4 (2023)	Year 5 (2024)	Year 6 (2025)
Expanded FH listing	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Non-FH high risk subgroups	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Total	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

Source: Table 4.2-6 (p 131), Table 4.2-7 (p 131) of the resubmission

Abbreviations: FH, familial hypercholesterolaemia

6.63 The resubmission estimated that the cumulative net cost across both populations would be more than \$100 million over six years.

6.64 The revised estimates provided in the pre-PBAC response estimated a cumulative net cost across both populations of more than \$100 million over six years.

Quality Use of Medicines

6.65 The resubmission suggested that the proposed listing allowing initiation by a general practitioner in consultation with a specialist physician would allow for appropriate attendance to the considerable increase in patient numbers potentially eligible for treatment with evolocumab. The resubmission argued that the complexity of the restriction and the nature of a written Authority would ensure that the expanded use of evolocumab was judiciously restricted to eligible populations, and that patients would be appropriately treated with statins and ezetimibe before being considered for evolocumab. The ESC considered that, while initiation by a specialist physician and a written initial Authority remained the most appropriate method of ensuring that appropriate statin and ezetimibe treatment occurred prior to evolocumab and that leakage was minimised, based on the volume of patients a written authority does not appear feasible.

6.66 The resubmission also stated that the sponsor would provide education tools for clinicians to assist in identifying and managing eligible patients.

Financial Management – Risk Sharing Arrangements

6.67 The resubmission noted there is currently a subsidisation cap arrangement in place for evolocumab based on forecast utilisation in FH patients (homozygous, heterozygous with ASCVD and LDL > 3.3 mmol/L, heterozygous without ASCVD and LDL > 5.0 mmol/L). Any expenditure over the caps is to be rebated in full. The resubmission stated that the sponsor is willing to agree to a revised arrangement for evolocumab which reflects total forecast utilisation under the current and proposed restriction and which will provide certainty as to the absolute maximum cost of evolocumab to the PBS. The new overall caps proposed in the resubmission are outlined in the table below.

Table 17: Proposed caps for the expanded listing (5 year deed period shown) (per resubmission)

	2020	2021	2022	2023	2024
Caps for current FH listing ^a	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Caps for current listing adjusted for higher rebate ^b	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Forecast expenditure for proposed new listings	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Proposed new overall caps	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 4.6-2 (p 132) of the resubmission

Abbreviations: FH, familial hypercholesterolaemia

^a For simplicity, caps for 1 November 2019 to 31 October 2020 under the current arrangement are taken to represent the 2020 calendar year under a new arrangement. Existing caps have been extended out a further year based on growth in expenditure in the year prior.

^b Simple adjustment x $(1 - \text{[REDACTED]}) / (1 - \text{[REDACTED]})$.

- 6.68 The pre-PBAC response revised the proposed overall cap to reflect: the lower price proposed for both the non-FH population and the expanded FH population; and the reduced proportion of patients who would meet the ESC's revised eligibility criteria for the non-FH population. The pre-PBAC response stated "The DUSC advice concluded that [the sponsor's] submission estimates were uncertain, but likely underestimates. In this respect, the revised analysis on which the proposed RSA caps are based is considered conservative. The proposed ■■■% rebate above the expenditure caps will provide certainty as to the maximum cost of this listing to the Commonwealth."

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

7 PBAC Outcome

- 7.1 The PBAC deferred making a recommendation on the listing of evolocumab for the treatment of non-familial hypercholesterolaemia (non-FH) in patients with atherosclerotic cardiovascular disease (ASCVD) and additional high-risk factors. The PBAC considered there were important clinical benefits associated with evolocumab therapy in appropriate high risk patient groups. However, the PBAC considered that the incremental cost-effectiveness ratio (ICER) was high, and that a price reduction would be required to bring the ICER into an acceptable range. Further, the PBAC considered that the total financial impact was high and represented a significant opportunity cost for the Commonwealth.
- 7.2 The PBAC also deferred making a recommendation on the resubmission's request to extend the existing familial hypercholesterolaemia (FH) listing to include patients with LDL levels >2.6 mmol/L (from >3.3 mmol/L). The PBAC considered that patients with FH who have symptomatic ASCVD and LDL-c levels over 2.6 mmol/L would have at least an equivalent lifetime risk to the non-FH population identified in the revised restriction. As such, the PBAC 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.
- 7.3 The PBAC considered that there is a moderate unmet clinical need for patients with non-FH with high cardiovascular risk who are not adequately controlled with available lipid-lowering therapies. The PBAC noted that the ESC had further defined the high-risk population subgroups (as outlined in Paragraph 2.4, and in the PBAC's suggested amendments to the restriction under Paragraph 2.1) and that the pre-PBAC response had accepted most of these changes. The PBAC considered that the revised restriction (outlined under Paragraph 2.1) had adequately defined the groups of patients who would derive most benefit from treatment with evolocumab.
- 7.4 The PBAC considered placebo, the nominated main comparator, to be appropriate.

- 7.5 The PBAC noted that the key clinical trial evidence presented to support the proposed non-FH listing was the FOURIER trial, which showed that evolocumab was associated with a statistically significant decreased risk of cardiovascular events compared with placebo (HR 0.85; 95% CI 0.79, 0.92). The PBAC also noted that evolocumab was associated with a 59% relative decrease in LDL-c levels compared with placebo (95% CI: 58%, 60%). The PBAC considered there was consistency in the results from FOURIER and trials of other lipid-lowering interventions such as the Cholesterol Treatment Trialists' Collaboration (CTTC) trials (statins ± ezetimibe) and ODYSSEY (alirocumab), and considered that the benefit of LDL-c lowering has been clearly established. The PBAC specifically noted that a 22% reduction in major adverse cardiovascular events (MACE) was observed for each 1.0 mmol/L reduction in LDL-c levels across large-scale meta-analyses (including CTTC 2005, 2010, 2012 and 2015).
- 7.6 The PBAC noted that no significant safety issues were identified and considered that the claim of non-inferior safety of evolocumab versus placebo was reasonable.
- 7.7 The pre-PBAC response presented a revised base case for the economic analysis that addressed many of the issues raised by the Commentary and the ESC, as outlined in Paragraph 6.48. The PBAC considered that most of the amendments were appropriate including: using a 25 year time horizon; applying a treatment discontinuation rate of 1% per cycle for the first 4 years; and basing the cardiovascular event rate and distribution of cardiovascular events on FOURIER data adjusted for high risk subgroups and a higher baseline LDL-c. However, the PBAC considered that the magnitude of the difference in baseline LDL-c between FOURIER and the proposed PBS population was incorrectly calculated, and that the modelling of the mortality benefit remained uncertain, as discussed below.
- 7.8 The pre-PBAC response (p1-2) adjusted the cardiovascular event rate for the estimated difference in baseline LDL-c between FOURIER and the proposed PBS population using an LDL-c difference of 0.93 mmol/L. However, this was derived using the median baseline LDL-c level observed in FOURIER. The PBAC considered that the mean value should have been used and noted that this would result in an LDL-c difference of 0.8 mmol/L (as outlined in Paragraph 6.48).
- 7.9 The pre-PBAC response (p1) applied a 3.6 year time lag between LDL reduction and impact on cardiovascular death, consistent with the previous submission (July 2018) and the March 2018 submission for the FH indication. The PBAC noted that there was no direct data from the FOURIER trial to support a mortality benefit over the median follow-up of 2.2 years. However, the PBAC considered that evolocumab would likely be associated with a reduction in cardiovascular mortality over a longer time period based on the observed lag in treatment effect on cardiovascular mortality in prior statin and alicumab studies. Further, the PBAC reiterated that it is biologically plausible for the mortality benefit of lipid-lowering therapy to become evident over a longer time period, as a reduction in LDL levels would first translate into plaque reduction or stabilisation, which then leads to reduced or delayed CV events, and

subsequently fewer deaths.

- 7.10 The PBAC considered that the pre-PBAC response's approach to modelling the mortality lag was more appropriate than the approach used in the resubmission (i.e. the PBAC considered that the 3.6 year mortality lag used in the pre-PBAC response was more appropriate than the 2 year lag with linear adjustment for 2 years used in the resubmission). However, the PBAC noted that there was no direct data to support the length of the time lag or the magnitude and duration of the reduction in cardiovascular mortality for evolocumab. As such, the PBAC considered that the most appropriate method to model the likely mortality benefits of evolocumab remained unclear and that this was a source of considerable uncertainty in the economic model. The PBAC noted that the inclusion of a mortality benefit was a key driver of the economic model.
- 7.11 The PBAC noted the pre-PBAC response offered a further price reduction which resulted in an ICER of \$15,000/QALY - \$45,000/QALY in the pre-PBAC response's revised base case. The PBAC noted the ICER increased to \$15,000/QALY - \$45,000/QALY if a more appropriate LDL-c adjustment (0.8 mmol/L) was applied. The PBAC considered this ICER remained too high in the context of a secondary prevention treatment with an unknown magnitude of mortality benefit (given the inclusion of a mortality benefit was a key driver of the economic model), and advised that an ICER less than \$15,000/QALY - \$45,000/QALY would be required for evolocumab to be considered suitably cost-effective. The PBAC also considered that an ICER less than \$15,000/QALY - \$45,000/QALY would be more consistent with previous decisions for secondary prevention medicines. The PBAC advised that this ICER should be based on the model submitted with the pre-PBAC response, but with a 0.8 mmol/L difference between the PBS and FOURIER trial populations.
- 7.12 The PBAC also requested that the sponsor provide data on the number of cardiovascular deaths, myocardial infarctions (MIs), strokes and other major cardiovascular events avoided in the economic model over the 25-year time horizon together with a comparison of the number of events avoided in the FOURIER trial.
- 7.13 The PBAC noted that the resubmission had estimated a cumulative net cost across both populations (i.e. the non-FH population and the expanded listing for patients with FH with LDL-c levels between 2.6 and 3.3 mmol/L) of more than \$100 million over six years, and that this was reduced to more than \$100 million over 6 years in the pre-PBAC response. Even with the reduced price and reduced patient numbers estimated in the pre-PBAC response, the PBAC considered that the total financial impact was high and considered that this represented a significant opportunity cost for the Commonwealth.
- 7.14 The PBAC noted that DUSC had identified a number of uncertainties with the financial estimates and had considered the financial impact of listing evolocumab was likely underestimated in the non-FH population. As such, the PBAC considered that the pre-

PBAC response's revised patient numbers were appropriate in the context of these estimates being used to implement an RSA with a [REDACTED] % rebate above the subsidy cap, and given the lack of more reliable alternative data on which to base the estimates.

7.15 The PBAC advised that a minor resubmission would be required that addresses the following issues:

- Include the updated restriction based on the PBAC's advice (i.e. per the amended restriction under Paragraph 2.1).
- A further price reduction would be required to achieve an ICER of less than \$15,000 - \$45,000 per QALY, using the pre-PBAC response economic model with a baseline LDL-c adjustment of 0.8 mmol/L. The PBAC advised that this lower price should also be applied to the additional FH population (i.e. patients with FH and atherosclerotic disease who have LDL levels between 2.6 and 3.3 mmol/L despite optimised treatment with statins and ezetimibe).
- The financial estimates should be revised to reflect the lower price (derived from the economic model outlined above).
- An RSA with a [REDACTED] % rebate above the caps would be required given the uncertain patient numbers and the potential for use outside the restriction.

Outcome:

Deferred

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

Amgen will continue to work with the PBAC to achieve PBS listing of evolocumab for patients with high risk atherosclerotic cardiovascular disease that is not adequately managed with currently available treatments.