

7.02 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

1 Purpose of Application

- 1.1 The current resubmission requested a Section 85 (Authority Required) PBS listing for evolocumab to include the treatment of non-familial hypercholesterolaemia with atherosclerotic disease. The PBAC has previously considered five submissions for evolocumab at the March 2015, March 2016, July 2017 (minor submission), November 2017 and March 2018 (minor submission) meetings.
- 1.2 Listing was requested on a cost-effectiveness basis compared to ezetimibe and placebo.

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

Component	Description
Population	Patients with non-familial hypercholesterolaemia with atherosclerotic cardiovascular disease who have not achieved target LDL levels despite treatment with maximal tolerated dose of a statin or who are statin-intolerant.
Intervention	Evolocumab 140 mg subcutaneous injection every fortnight or evolocumab 420 mg subcutaneous injection every month.
Comparator	Ezetimibe 10 mg oral tablet once daily, placebo, alirocumab 75 to 150 mg subcutaneous injection every fortnight or alirocumab 300 mg subcutaneous injection every month.
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 ezetimibe, Evolocumab is superior in terms of efficacy and inferior in terms of safety compared to placebo, No clinical claim was made for the comparison of evolocumab and alirocumab ^a .

Source: Table 1.1.1 (p 13) of the resubmission

^a The sponsor has previously claimed that evolocumab is at least non-inferior in terms of efficacy (LDL outcomes) and similar in terms of safety compared to high dose (150 mg fortnightly) alirocumab (November 2017 Evolocumab Public Summary Document).

2 Requested listing

- 2.1 The changes to the proposed listing from November 2017 for the non-familial hypercholesterolaemia population are highlighted below in grey; these changes relate to the criteria defining statin intolerance.

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 Sureclick® Amgen
Evolocumab, 120 mg/mL injection, 3.5 mL injection device	1	1	5	\$ [REDACTED] (\$ [REDACTED])	Repatha Automated Mini-Doser® Amgen
Category/Program:	General Schedule				
PBS indication:	Hypercholesterolaemia				
Restriction:	Authority Required				
Clinical criteria:	<p>The treatment must be in conjunction with dietary therapy and exercise AND Patient must have symptomatic coronary heart disease; OR Patient must have symptomatic cerebrovascular disease; OR Patient must have symptomatic peripheral vascular disease. AND Patient must have an LDL cholesterol level in excess of 3.3 millimoles per litre after at least 3 months of treatment at a maximum tolerated dose of an HMG CoA reductase inhibitor (statin), in conjunction with dietary therapy and exercise; OR Patient must have an LDL cholesterol level in excess of 3.3 millimoles per litre after having developed a clinically important product-related adverse event during treatment with an HMG CoA reductase inhibitor (statin) necessitating a withdrawal of statin treatment; OR Patient must have an LDL cholesterol level in excess of 3.3 millimoles per litre and must be one in whom treatment with an HMG CoA reductase inhibitor (statin) is contraindicated.</p>				
Treatment criteria:	<p>Must be treated by a consultant physician or in consultation with a consultant 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>The date of the consultation with a consultant physician must be no more than 6 months prior to the application for a PBS authority. The full name of the consultant 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. With the exception of patients contraindicated to a statin, the agent, dose and duration of statin treatment must be provided at the time of application.</p> <p>Maximum tolerated dose determined as: for patients not on the highest possible statin dose (i.e. 80mg atorvastatin or 40mg rosuvastatin), clinicians must confirm that a higher dose statin has been trialled and not tolerated. For patients intolerant of statin therapy, the agents, doses and duration of treatment and adverse events experienced with at least 2 statins must be provided at the time of application. For patients contraindicated to statin therapy, details of the contraindication must be provided at the time of the application.</p> <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>c) The date of consultation and the full name of the consultant physician; and</p> <p>d) Details of the diagnosis of symptomatic coronary heart, cerebrovascular or peripheral vascular disease; and</p> <p>e) 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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Note: Amendments to the proposed restriction are shaded.

- 2.2 The resubmission proposed a special pricing arrangement consisting of a [REDACTED] % rebate on government expenditure for non-familial hypercholesterolaemia. This is a larger rebate than previously proposed for non-familial hypercholesterolaemia ([REDACTED] % rebate, November 2017 submission), heterozygous familial hypercholesterolaemia ([REDACTED] % rebate, March 2018 minor submission) and homozygous familial hypercholesterolaemia ([REDACTED] % rebate, current listing).
- 2.3 The main change in the proposed restriction compared to the November 2017 submission was the addition of treatment criteria that defined the maximum tolerated statin dose as atorvastatin 80 mg or rosuvastatin 40 mg. Patients requiring lower doses are expected to trial at least two statins with documentation of any contraindication or intolerance. As per similar changes proposed in the March 2018 minor submission, the PBAC advised that for those patients intolerant to statins, the restriction should be amended to include a trial of ezetimibe treatment. In addition, for patients who could 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.
- 2.4 The proposed restriction does not adequately address previous PBAC concerns regarding the inadequate definition of atherosclerotic disease, inadequate justification of the LDL threshold or the lack of identification of potential subgroups who would most benefit from PCSK9 inhibitors. The PBAC and ESC were concerned that there was a high risk of use outside the restriction if the population most likely to benefit was not clearly defined. This would have implications on the cost-effectiveness, utilisation and financial estimates.
- 2.5 The Pre-Sub-Committee Response (PSCR) identified three subgroups which were at highest risk of subsequent cardiovascular events; patients with: previous MI, previous ischemic stroke and previous symptomatic peripheral arterial disease. The ESC considered that based on the data presented in the PSCR, these 'subgroups' accounted for almost all of the ASCVD population.
- 2.6 The pre-PBAC response reiterated the request for input from the PBAC regarding the subpopulations that would benefit most. The pre-PBAC response did propose that individuals with both uncontrolled LDL (despite maximum tolerated statin and/or ezetimibe) and specific events might be appropriate to consider as target populations. The specific events included:

- previous MI, as this population is most likely to have event recurrence;
 - patients with established cardiovascular disease and one or more specified risk factors (e.g. diabetes, peripheral arterial disease, multi-vessel disease);
 - symptomatic peripheral arterial disease. This population was well-defined within the FOURIER trial and could be identified by ABI score (e.g. < 0.85); and
 - cardiovascular risk in Aboriginal and Torres Strait islander people.
- 2.7 The ESC noted that high risk subgroups (e.g. those with more recent MI, multiple prior MIs and residual multi-vessel coronary artery disease) identified in a published analysis of the FOURIER trial (Sabatine, 2018¹) as likely to receive a greater benefit from treatment with evolocumab were not identified in the resubmission, the PSCR or the Pre-PBAC response (see Comparative effectiveness section below).
- 2.8 The PSCR stated that the LDL threshold of 3.3 mmol/L proposed in the restriction was adopted as it matched the clinical criteria already recommended by the PBAC for familial hypercholesterolaemia, despite recent data indicating that a threshold of 2.6 mmol/L may be more clinically appropriate for high risk cardiovascular patients. The ESC noted that the FOURIER trial adopted a LDL threshold of 1.8 mmol/L. Subgroup analyses (Sabatine, 2017²) suggested that higher baseline LDL levels trended towards less impact on primary and secondary outcomes (see Comparative effectiveness section below).
- 2.9 The pre-PBAC response suggested that targeting a higher LDL threshold would result in more events avoided and a higher LDL threshold was therefore requested as there is a higher clinical need to treat this population and reduce the risk of events.
- 2.10 The PBAC noted that the population and eligibility criteria in the proposed PBS restriction, the PSCR and the pre-PBAC response remained inadequately defined.

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

3 Background

Registration status

- 3.1 Evolocumab was approved by the TGA on 4 December 2015 for the treatment of:
- Adults with heterozygous familial hypercholesterolaemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD):

¹ Sabatine MS, De Ferrari GM, Giugliano RP, et al. "Clinical benefit of evolocumab by severity and extent of coronary artery disease: an analysis from FOURIER." *Circulation*, 2018, 6 April: doi:10.1161/CIRCULATIONAHA.118.

² Sabatine MS, Giugliano RP, Keech AC, et al. "Evolocumab and clinical outcomes in patients with cardiovascular disease" *NEJM*, 2017: 376; 1713-1722.

- in combination with a statin or statin with other lipid lowering therapies,
- in combination with other lipid-lowering therapies in patients who are statin-intolerant.
- Homozygous familial hypercholesterolaemia (HoFH):
 - in combination with other lipid lowering therapies in adults and adolescents aged 12 years and over.

The current TGA indication notes that the effect of evolocumab on cardiovascular morbidity and mortality has not yet been determined.

- 3.2 The sponsor was seeking a revision of the TGA indication to include a broader population (any patient with hypercholesterolaemia OR atherosclerotic cardiovascular disease OR at risk of atherosclerotic cardiovascular disease) based on the availability of cardiovascular outcome data. The sponsor also requested TGA approval for evolocumab as a monotherapy agent. The proposed revision is expected to be considered by the TGA in August 2018. The First Round TGA Clinical Evaluator's report for the revised indication was available during the evaluation. The Delegate's Overview became available following the ESC meeting.
- 3.3 The first round TGA clinical evaluator's report noted that FOURIER trial results supported a reduction in cardiovascular morbidity with evolocumab treatment but did not adequately support a reduction in cardiovascular mortality. The TGA evaluator noted that this benefit has only been demonstrated in adult patients with established cardiovascular disease who were using moderate to high intensity statins. The TGA evaluator stated that the benefit-risk balance in the proposed usage is currently not favourable, as the proposed indication does not reflect the patient population in which efficacy and safety were demonstrated.
- 3.4 The Delegate's Overview noted that the primary and secondary composite outcomes of the FOURIER trial were driven by MI and stroke with no statistically significant difference between evolocumab and placebo for cardiovascular, coronary or all-cause mortality.

Previous PBAC consideration

- 3.5 The outstanding matters of concerns from the previous November 2017 PBAC meeting are summarised in the table below.

Table 2: Summary of outstanding matters of concern

Matter of concern	How the resubmission addresses it
<p>The PBAC did not recommend the listing of evolocumab for patients with non-familial hypercholesterolaemia with atherosclerotic disease on the basis of a high incremental cost effectiveness ratio and high and uncertain patient population numbers [7.1 November 2017 PSD].</p>	<p>The resubmission proposed a larger government rebate on the cost of evolocumab (from █████% to █████%) which resulted in a lower effective price and an improved cost effectiveness ratio for the treatment of non-familial hypercholesterolaemia with atherosclerotic disease (current ICER vs ezetimibe: \$█████ per QALY, previous ICER vs ezetimibe: \$█████ per QALY).</p> <p>The PBAC and ESC considered that the resubmission did not adequately address uncertainty in patient population numbers (size of population meeting eligibility criteria, market growth rates, uptakes rates, replacement of non-statin therapies other than ezetimibe).</p>
<p>The PBAC acknowledged there is a high unmet clinical need for patients with non-FH and ASCVD who are not adequately controlled with available lipid-lowering therapies, but considered that this population was inadequately defined. The PBAC advised further modelling could be used to determine the qualifying LDL-c level for the non-FH population with ASCVD, and the proposed PBS restriction would require more specific definitions of ASCVD and statin intolerance [7.12 November 2017 PSD].</p>	<p>The resubmission proposed additional treatment criteria to the requested restriction that defined maximum tolerated statin dose as atorvastatin 80 mg or rosuvastatin 40 mg. Patients requiring lower doses are expected to trial at least two statins with documentation of any contraindication or intolerance.</p> <p>The PBAC and ESC considered that the proposed restriction did not adequately address previous PBAC concerns regarding the definition of atherosclerotic disease or the justification of the LDL threshold. The ESC noted the published subgroup analyses of the FOURIER trial by LDL at baseline in Sabatine, 2017.</p>
<p>The PBAC noted the pre-PBAC response suggested a stakeholder meeting to discuss the role of PCSK9 inhibitors in the wider population. However, the PBAC was reluctant to enter into such discussions without greater clarity and agreement about the non-FH population who would most benefit from PCSK9 inhibitors and without further economic modelling of the cost-effectiveness and opportunity cost of a broader listing upon which to base such discussions. The PBAC also noted that outcome data for alirocumab is not yet available and would also be needed to inform such discussions [7.13 November 2017 PSD].</p>	<p>No change.</p> <p>The PBAC and ESC considered that the proposed restriction does not adequately address previous PBAC concerns about the identification of potential subgroups that would most benefit from PCSK9 inhibitors. The ESC noted the published subgroup analyses of the FOURIER trial by level of risk published in Sabatine, 2018.</p> <p>Top-line results from the key cardiovascular outcome study for alirocumab (ODYSSEY OUTCOMES) became available during the evaluation.</p>
<p>The PBAC noted the FOURIER trial population was more aligned with the non-FH population with ASCVD and that these trial data could be used to better inform the economic model. As with the FH population, more conservative assumptions about the time to CV mortality benefit should be included in a future economic model [7.14 November 2017 PSD].</p>	<p>The resubmission introduced a █████ year time lag between LDL reduction and impact on cardiovascular death in the economic model.</p> <p>There was no change in the use of FOURIER data in the economic model (directly informs LDL changes with evolocumab and indirectly supports relationship between LDL and cardiovascular outcomes). The PBAC and ESC considered the resubmission does not adequately address previous PBAC concerns about better use of FOURIER data in the economic model (e.g. potential use as data inputs, trial based economic analysis using cardiovascular outcomes, validation of model estimates).</p>

Matter of concern	How the resubmission addresses it
<p>The PBAC noted the very high financial impact of extending the listing beyond the FH population and noted the DUSC raised considerable uncertainty in the estimates and likelihood of growth in the market. The PBAC considered a risk-share arrangement to manage the financial risks, including hard caps with 100% rebates, would need to be considered [7.15 November 2017 PSD].</p>	<p>The resubmission proposed a lower effective price which reduced the overall budget impact of listing evolocumab for non-familial hypercholesterolaemia with atherosclerotic disease (cumulative net cost over 6 years reduced from \$██████ to \$██████).</p> <p>The resubmission proposed a tiered risk share arrangement which included additional rebates for government expenditure exceeding predicted estimates.</p> <p>The ESC considered the submission has not adequately addressed uncertainty in patient population numbers (size of population meeting eligibility criteria, market growth rates, uptakes rates, replacement of non-statin therapies other than ezetimibe).</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 condition characterised by elevated serum cholesterol levels and is associated with the development of atherosclerosis and an increased incidence of angina, myocardial infarction, stroke, coronary artery disease and peripheral vascular disease.
- 4.2 The target population in the resubmission is the subset of non-familial hypercholesterolaemia patients with pre-existing atherosclerotic disease who have not achieved target LDL levels despite use of available hypercholesterolaemia treatments.
- 4.3 The resubmission claimed that evolocumab would replace or be used in addition to other non-statin therapies for hypercholesterolaemia.

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

5 Comparator

- 5.1 The resubmission nominated both ezetimibe (most widely used non-statin therapy) and placebo as the main comparators. Although in November 2017, the PBAC considered this was appropriate for the combined familial and non-familial hypercholesterolaemia submission, at the July 2018 meeting the PBAC were concerned that by nominating ezetimibe as a comparator, ezetimibe could be replaced in the treatment algorithm by evolocumab.
- 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) with overlapping indications. In November 2017, the PBAC considered this was appropriate.

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 one health care professional via the Consumer Comments facility on the PBS website which supported the listing of evolocumab on the basis of allowing patients to safely attain lower LDL cholesterol.

Clinical trials

6.3 The resubmission was based on a series of comparisons between evolocumab and nominated comparators, that have all previously been considered by PBAC:

- One head-to-head comparison of cardiovascular outcomes with evolocumab versus placebo in hypercholesterolaemia patients with atherosclerotic cardiovascular disease (FOURIER) including an additional safety sub-study investigating neurocognitive effects (EBBINGHAUS).
- One head-to-head comparison of atherosclerotic plaque burden with evolocumab versus placebo in hypercholesterolaemia patients with evidence of coronary disease (GLAGOV).
- Direct comparison of lipid outcomes with evolocumab versus placebo or ezetimibe in various hypercholesterolaemia populations (FOURIER, GLAGOV, GAUSS-2, GAUSS-3, RUTHERFORD-2, LAPLACE-2, MENDEL-2, DESCARTES).
- Indirect comparison of lipid outcomes with evolocumab versus alirocumab in various hypercholesterolaemia populations. This comparison was considered as a supportive analysis during the evaluation with only summary details presented.

6.4 During the evaluation, top-line results from the key cardiovascular outcome study for alirocumab (ODYSSEY OUTCOMES) became available and were included. There was insufficient information available during the evaluation to conduct a formal indirect analysis of cardiovascular outcomes between evolocumab and alirocumab.

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

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
20110114 (MENDEL-2)	Amgen Clinical Study Report (2014). 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	Internal study report
	Koren MJ et al (2014). Anti-PCSK9 monotherapy for hypercholesterolaemia: The MENDEL-2 randomized, controlled phase III clinical trial of evolocumab	Journal of the American College of Cardiology 63: 2531–2540
20110115 (LAPLACE-2)	Amgen Clinical Study Report (2014). 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.	Internal study report
	Robinson JG et al (2014). 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	Journal of the American Medical Association 311: 1870–1882
20110116 (GAUSS-2)	Amgen Clinical Study Report (2014). 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	Internal study report
	Stroes E et al (2014). Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: The GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab	Journal of the American College of Cardiology 63: 2541–2548
20110117 (RUTHERFORD-2)	Amgen Clinical Study Report (2014). 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.	Internal study report
	Raal F et al (2015). PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial.	Lancet 9965: 331–340
20110109 (DESCARTES)	Amgen Clinical Study Report (2014). 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	Internal study report
	Blom D et al (2014). A 52-week placebo-controlled trial of evolocumab in hyperlipidemia.	New England Journal of Medicine 370:1809–1819
20120332 (GAUSS-3)	Amgen Clinical Study Report (2016). 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	Internal study report
	Nissen SE et al (2016). Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance. The GAUSS-3 randomised clinical trial	Journal of the American Medical Association 315: 1580–1590

Trial ID	Protocol title/ Publication title	Publication citation
20110118 (FOURIER)	Amgen Clinical Study Report (2017). 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	Internal study report
	Sabatine MS et al (2017). Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease	New England Journal of Medicine 376: 1713-1722
20130385 (EBBINGHAUS)	Amgen Clinical Study Report (2017). A Double-Blind, Placebo Controlled, Multicenter Study to Assess the Effect of Evolocumab on Cognitive Function in Patients with Clinically Evident Cardiovascular Disease and Receiving Statin Background Lipid Lowering Therapy: A Study for Subjects Enrolled in the FOURIER (Study 20110118) Trial	Internal study report
	Giugliano et al (2017). Cognitive Function in a Randomized Trial of Evolocumab	New England Journal of Medicine 377: 633-643
20120153 (GLAGOV)	Amgen Clinical Study Report (2016). 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	Internal study report
	Nicholls SJ et al (2016). Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients. The GLAGOV Randomised Clinical Trial	Journal of the American Medical Association 316: 2373-2384
ODYSSEY OUTCOMES	Schwartz GG et al (2014). 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	American Heart Journal 168: 682-689
	Schwartz GG et al (2018). The ODYSSEY OUTCOMES Trial: Topline Results Alirocumab in Patients After Acute Coronary Syndrome	American College of Cardiology – 67th Scientific Sessions March 10, 2018 (Session 401)

Source: Table 2.2-1 (p 31-39) of the resubmission; Table 2 (p 4--10) Attachment 5 of the resubmission

Note: Only includes the main publications for each trial

6.6 The key features of the included studies are summarised in the table below.

Table 4: Key features of the included evidence (evolocumab versus placebo)

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
MENDEL-2	615	MC, R, DB, AC, PC 12 week duration	Low	Low-risk patients requiring monotherapy	Lipid parameters	Not used
LAPLACE-2	2,067	MC, R, DB, AC, PC 12 week duration	Low	Patients requiring combination with statin	Lipid parameters	Not used
GAUSS-2	307	MC, R, DB, AC 12 week duration	Low	Statin-intolerant patients	Lipid parameters	Not used
RUTHERFORD-2	331	MC, R, DB, PC 12 week duration	Low	Heterozygous familial hypercholesterolaemia	Lipid parameters	Not used
DESCARTES	905	MC, R, DB, PC 52 week duration	Low	Patients failing current therapies	Lipid parameters	Not used
GAUSS-3	218	MC, R, DB, AC 24 week duration	Low	Statin-intolerant patients	Lipid parameters	Not used
FOURIER	27,564	MC, R, DB, PC Median 2.2 year duration	Low	Hypercholesterolaemia with atherosclerotic disease	Cardiovascular events, lipid parameters	Used to support relationship between LDL and cardiovascular events
EBBINGHAUS Sub-study	1,974	Nested sub-study of FOURIER	Low	Hypercholesterolaemia with atherosclerotic disease	Neurocognitive measures	Not used
GLAGOV	970	MC, R, DB, PC 78 week duration	Low	Hypercholesterolaemia with atherosclerotic disease	Intravascular imaging outcomes	Not used
ODYSSEY OUTCOMES	18,924	MC, R, DB, PC Median 2.8 year duration	Low	Hypercholesterolaemia with recent acute coronary syndrome	Cardiovascular events, lipid parameters	Not used

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

Source: Table 2.2-1 (p 31-39), Table 2.3-1 (p 41-42), Table 2.4-1 (p 44) of the resubmission; Table 2 (p 4--10) Attachment 5 of the resubmission; Schwartz (2014) publication; Schwartz (2018) ACCC presentation

Comparative effectiveness

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

Table 5: Key cardiovascular time to event analyses reported in the FOURIER trial (median 2.2 year duration)

Outcome	Evolocumab N = 13,784	Placebo N = 13,780	Hazard ratio (95% CI)
Composite outcomes (first event only)			
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)
Cardiovascular death, myocardial infarction, or stroke	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			
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; Bold text = statistically significant or nominally significant result

Source: Table 2.5-1 (p 54-55) 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

- 6.8 Treatment with evolocumab was associated with a decreased risk of myocardial infarction, coronary revascularisation and ischaemic stroke compared to placebo. There was no apparent difference in angina, coronary death, cardiovascular death or all-cause mortality between treatment arms. In the FOURIER trial, treatment with evolocumab was associated with a 59% relative decrease and a 1.38 mmol/L absolute decrease in LDL levels compared to placebo.
- 6.9 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.
- 6.10 The FOURIER trial report noted some differences in treatment effects across patient subgroups defined by race, geographic location and previous history of myocardial infarction.
- 6.11 In the high risk subgroups identified in Sabatine, 2018, among patients with prior MI, those with a more recent MI, multiple prior MIs, or residual multi-vessel coronary artery disease were at higher risk of cardiovascular events and tended to experience greater and earlier cardiovascular risk reduction LDL-C lowering with evolocumab.

The relative risk reductions with evolocumab for the primary end point were 20% (HR = 0.80; 95% CI: 0.71, 0.91), 18% (HR = 0.82; 95% CI: 0.72, 0.93) and 21% (HR = 0.92; 95% CI: 0.84, 1.02) for those with more recent MI, multiple prior MIs and residual multi-vessel coronary artery disease; whereas they were 5% (HR = 0.95; 95% CI: 0.85, 1.05), 8% (HR = 0.92; 95% CI: 0.84, 1.02) and 7% (HR = 0.93; 95% CI: 0.85, 1.02) in those without, respectively. Given the higher baseline risk, the respective absolute risk reductions at 3 years exceeded 3% in the high risk groups (3.4%, 3.7% and █%) versus approximately 1% in the low risk groups (0.8%, 1.3% and 1.2%). The primary end point was a composite of CV death, MI, stroke, hospitalisation for unstable angina or coronary revascularisation.

- 6.12 FOURIER subgroup analyses published in Sabatine, 2017 suggested that higher baseline LDL levels did not identify a population where there was a greater treatment effect for the primary endpoint:
- LDL < 2.1 mmol/L: HR = 0.80 (95% CI: 0.69, 0.93), n = 6,961;
 - LDL 2.1 mmol/L to < 2.4 mmol/L: HR = 0.82 (95% CI: 0.71, 0.96), n = 6,886;
 - LDL 2.4 mmol/L to < 2.8 mmol/L: HR = 0.89 (95% CI: 0.77, 1.03), n = 6,887;
 - LDL > 2.8 mmol/L: HR = 0.89 (95% CI: 0.77, 1.02); n = 6,829.
- 6.13 The PSCR suggested that for those patients at high clinical risk, the FOURIER mortality data and population are less relevant, and the LDL impacts (mean LDL-c in FOURIER was 2.53 mmol/L) are important in the context of the known relationship between LDL and morbidity and mortality.
- 6.14 The results of the ODYSSEY OUTCOMES trial were generally supportive of the claims presented in the resubmission as alirocumab (another PCSK9 inhibitor) was associated with a reduction in cardiovascular events compared to standard care (time to first cardiovascular event of cardiovascular death, myocardial infarction, ischaemic stroke or hospitalisation for unstable angina; HR 0.85, 95% CI 0.78, 0.93).
- 6.15 Cardiovascular imaging results from the GLAGOV trial indicated that treatment with evolocumab was associated with a statistically significant reduction in atheroma volume over time compared to placebo (least squares mean change in percent atheroma volume -0.96 vs 0.05; treatment difference -1.01; 95% CI -1.38, -0.64).
- 6.16 LDL results from the lipid trials demonstrated that treatment with evolocumab (fortnightly and monthly dosing) was associated with statistically significant decreases in LDL levels compared to ezetimibe (approximately 40% reduction) and placebo (approximately 60% reduction) in mixed hypercholesterolaemia populations.
- 6.17 The resubmission claimed that the indirect analyses indicate that treatment with evolocumab was associated with a statistically significantly larger reduction in LDL levels compared to alirocumab. However, the resubmission also acknowledged the results of alternative indirect analyses presented in the November 2017 commentary. The analyses indicate that treatment with evolocumab was associated

with a statistically significantly larger reduction in LDL levels compared to lower-dose alirocumab treatment regimens (75 mg fortnightly, 300 mg monthly) but no statistically significant difference between evolocumab and higher dose alirocumab treatment regimens (150 mg fortnightly, titration 75-150 mg fortnightly).

Comparative harms

- 6.18 The most frequently reported adverse events with evolocumab were musculoskeletal disorders (myalgia, pain in extremity, muscle spasms, arthralgia, back pain), infections (nasopharyngitis, upper respiratory tract infection, influenza), general disorders and administration site conditions (fatigue, injection site reactions), gastrointestinal disorders (diarrhoea, nausea, constipation) and nervous system disorders (headache).
- 6.19 In regards to adverse events of special interest, treatment evolocumab was associated with a higher incidence of mild to moderate hypersensitivity reactions and injection site reactions compared to placebo.
- 6.20 There was no statistically significant difference in neurocognitive measures between evolocumab and placebo for patients enrolled in the EBBINGHAUS sub-study.
- 6.21 Available comparative safety data did not clearly favour evolocumab, ezetimibe or placebo. There was insufficient data presented in the resubmission to adequately assess the comparative safety of evolocumab and alirocumab.
- 6.22 An expanded assessment of harms did not identify any important risks with evolocumab treatment. Important potential risks included hypersensitivity reactions and immunogenicity (i.e. development of anti-evolocumab antibodies). Missing information for evolocumab included the long-term effects of exposure to low LDL levels (< 1 mmol/L).

Benefits/harms

- 6.23 On the basis of direct evidence presented in Table 5, for every 1,000 patients with hypercholesterolaemia with atherosclerotic disease treated with evolocumab in comparison to placebo over a mean duration of 2 years:
- approximately 12 (i.e. 46 - 34) fewer patients would have a myocardial infarction;
 - approximately 4 (i.e. 19 - 15) fewer patients would have an ischaemic stroke;
 - approximately 15 (i.e. 70 - 55) fewer patients would require coronary revascularisation;
 - there would be no apparent difference in cardiovascular deaths; and
 - there would be no apparent difference in adverse events.
- 6.24 On the basis of direct evidence presented in the resubmission, the comparison of evolocumab and placebo in patients with hypercholesterolaemia resulted in:
- a reduction in LDL levels of approximately 60%; and

- no apparent difference in adverse events
- 6.25 On the basis of direct evidence presented in the resubmission, the comparison of evolocumab and ezetimibe in patients with hypercholesterolaemia resulted in:
- a reduction in LDL levels of approximately 40% ; and
 - no apparent difference in adverse events
- 6.26 Current data are inadequate to reliably quantify the comparative benefits and harms of evolocumab and alirocumab.

Clinical claim

- 6.27 The resubmission described evolocumab as superior in terms of efficacy and similar in terms of safety compared to placebo, based on current data available.
- 6.28 The resubmission described evolocumab as superior in terms of efficacy (based on surrogate outcome measures) and similar in terms of safety compared to ezetimibe, based on indirect data.
- 6.29 The PBAC reiterated that whilst these claims may be reasonable for LDL reduction, and time to first MI, ischemic stroke or cardiac revascularisation based on the FOURIER trial data presented above, the PBAC and ESC noted the patient populations that could benefit most from treatment and be used to inform cost-effectiveness analyses were not identified in the submission or PSCR.
- 6.30 The ESC considered extrapolating that a reduction in subsequent cardiovascular events would result in an improvement in global health outcomes as was accepted for the familial hypercholesterolaemia group may not be reasonable, particularly as the real world population being considered for this requested listing were a diverse population, likely older, multi-morbid and who may have multiple other factors that would affect global health outcomes.
- 6.31 No clinical claim was made for the comparison of evolocumab and alirocumab. The PBAC has previously stated that the efficacy and safety of evolocumab compared to alirocumab was uncertain.

Economic analysis

- 6.32 The resubmission presented a stepped economic evaluation of evolocumab for the treatment of non-familial hypercholesterolaemia with atherosclerotic disease either as a replacement to ezetimibe or as an add-on to existing therapies. The economic evaluation was based on relative LDL reductions from the clinical trials and other modelled variables. The resubmission did not use cardiovascular outcome data from the FOURIER trial in the economic evaluation. The ESC considered that incorporation of FOURIER trial data into the economic model would have been informative; providing validation of model predictions to available observed data. In the pre-PBAC response it was noted that the proposed PBS population differed from the FOURIER

population in terms of LDL levels and therefore incorporation of the trial patients into the model was argued to be inappropriate.

- 6.33 Key changes to the economic model included a reduction in the proposed effective price for evolocumab (with a subsequent improvement in the estimated cost effectiveness ratio) and the incorporation of a [REDACTED] year time lag between LDL reduction and impact on cardiovascular death. This time lag was consistent with the March 2018 PBAC submission for the heterozygous familial hypercholesterolaemia population. In March 2018 the PBAC noted that secondary prevention trials with statins have either shown no mortality benefit or have indicated a lag in mortality benefit of at least two years. The ESC noted that although a [REDACTED] year time lag was accepted by the PBAC for patients with familial hypercholesterolaemia and that the incorporation of a lag into the model was reasonable, there was no direct data to support time lag of [REDACTED] years in non-familial hypercholesterolaemia. The ESC was also concerned that the association between LDL reduction and impact on cardiovascular mortality might differ between patients with familial and non-familial hypercholesterolaemia. The pre-PBAC response stated that there was also no evidence to suggest that an alternative lag would be more reasonable and suggested for those patients at high cardiovascular risk who have suffered a previous event, the likelihood of a subsequent event was an imminent risk, reducing, or even removing, the need for a time lag.

Table 6: 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. The ESC considered this time horizon may not be appropriate for non-familial hypercholesterolaemia.
Methods used to generate results	Markov cohort expected value analysis (with half-cycle correction)
Treatments	Evolocumab, ezetimibe, placebo
Health states	Five health states: baseline health state, 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 a CHD death and the probability that a non-fatal event is an MI or stroke. Probability of a cardiovascular event and 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

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

Source: Table 3.1-1 (p 100) of the resubmission

- 6.34 All patients start in the baseline health state. 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.

6.35 Key drivers of the economic model are summarised in the table below.

Table 7: Key drivers of the model

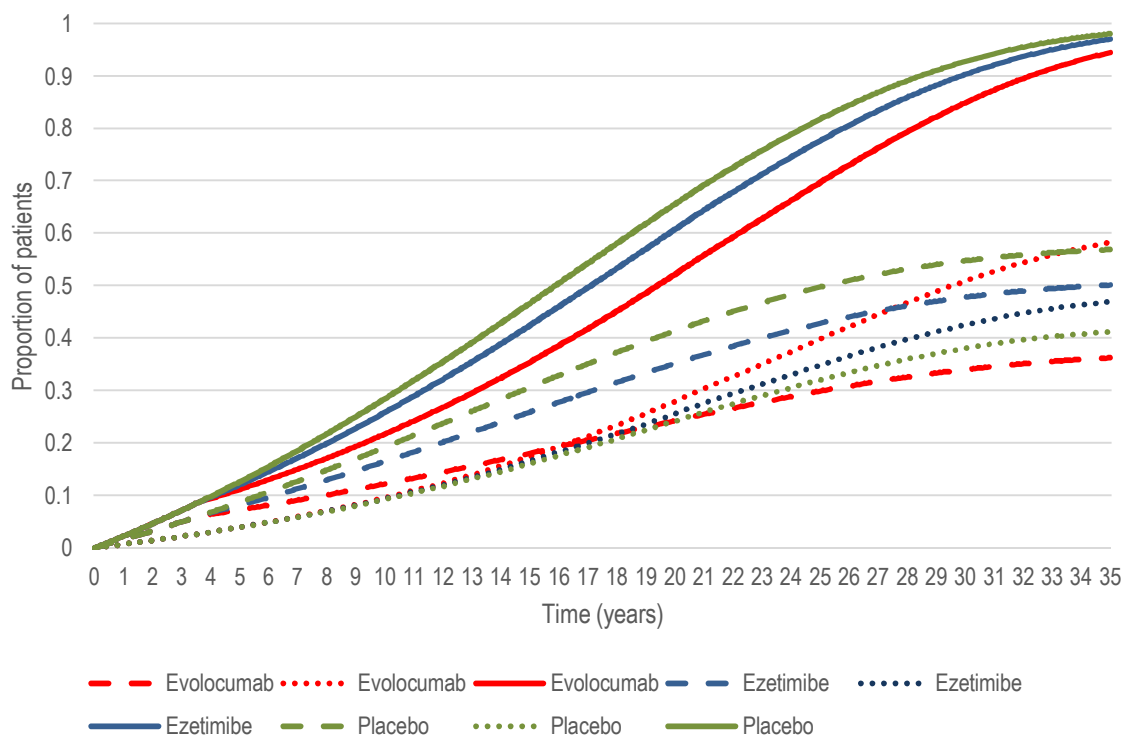
Description	Method/Value	Impact
Treatment effect on coronary death	<p>The resubmission assumed a ■■■ year time lag between LDL reduction and impact on coronary death. The resubmission did not adequately justify the time lag duration.</p> <p>After the initial time lag, the resubmission assumed substantial reductions in coronary death with active treatments based on modelled baseline LDL levels, trial-based estimates of LDL reduction, and the CTTC analysis quantifying the relationship between LDL levels and cardiovascular outcomes. The approach used in the model resulted in a substantially larger reduction in coronary death with evolocumab treatment compared to the FOURIER trial (modelled RR 0.45 vs observed HR 1.02; 95% CI: 0.82, 1.25, i.e. not statistically significant). A detailed breakdown of cardiovascular deaths from the FOURIER trial indicated that the incidence of death due to myocardial infarction and death due to stroke were numerically lower in the evolocumab treatment arm but these represented only a minority of cardiovascular deaths. Treatment with evolocumab did not appear to have any impact on sudden cardiac death (which represented the majority of fatalities in the FOURIER trial) or death from other cardiovascular causes.</p> <p>Published economic analysis incorporating FOURIER data were substantially more conservative than the resubmission. The Fonarow (2017) publication assumed no improvement in cardiovascular death for the first five years and then a moderate improvement in subsequent years (RR 0.90 per 1.0 mmol/L), compared to RR 0.78 per 1.0 mmol/L reduction in LDL in the submission's model. Alternatively, the Kazi (2017) publication assumed that evolocumab had no effect on cardiovascular death except as a direct result of lowering myocardial infarction or stroke risk.</p>	High favours evolocumab
Baseline LDL levels	The resubmission assumed that the LDL eligibility criterion (> 3.3 mmol/L) for PBS populations with atherosclerotic disease would result in a mean baseline LDL level of 5.5 mmol/L. The baseline LDL assumption was not justified in the resubmission and therefore it was unclear whether it was representative of the target PBS populations.	High, favours evolocumab
Distribution of cardiac events	<p>The resubmission estimated the distribution of cardiac events (myocardial infarction: 38.8%; ischaemic stroke 27.7%; coronary death 34.5%) based on the Heart Protection Study. The Heart Protection Study was a randomised controlled trial comparing simvastatin with placebo in previously <u>untreated</u> hypercholesterolaemia patients recruited between 1994 and 1997 with coronary disease, other occlusive arterial disease, or diabetes (5 year trial).</p> <p>The Heart Protection Study is unlikely to be representative of the target PBS populations. The resubmission did not adequately justify using these estimates instead of a distribution of events from the FOURIER trial. The FOURIER trial is likely to be more representative of current clinical practice, with recent clinical data and a patient population using moderate-to-high intensity statin background therapy with or without ezetimibe (2.2 year median duration). The most closely comparable distribution of events reported in the FOURIER trial for the placebo arm was: myocardial infarction: 62.0%, stroke: 23.5%, cardiovascular death 14.5%).</p> <p>The ESC noted that the difference in health outcomes, which was driven by the rate of coronary death (34.5% in the model versus 14.5% in the FOURIER trial), remained unchanged in the resubmission.</p>	High, favours evolocumab

Description	Method/Value	Impact
Treatment adherence	<p>The resubmission estimated treatment compliance for evolocumab based on the proportion of patients discontinuing treatment in the FOURIER trial. The resubmission assumed all treatments would have perfect persistence. Treatment with ezetimibe was assumed to have the same adherence patterns as evolocumab.</p> <p>The approach used to estimate adherence rates in the economic model was inappropriate as discontinuation rates are a measure of persistence rather than compliance. The available clinical data does not support the assumption of perfect persistence. The pre-PBAC response stated that the base case assumed adherence and persistence that was the same as that in the evolocumab treatment arm in the FOURIER trial and that the model allowed for patients to move to 'off treatment', where there were no drug costs and the effects of cholesterol lowering were immediately lost.</p> <p>It was unclear whether it is reasonable to assume no difference in adherence measures between active treatments given the differences in efficacy, mode of administration and frequency of dosing.</p> <p>The economic model implemented the compliance estimates as a flat reduction in drug costs. This was not appropriate as non-compliance would affect both costs and health outcomes.</p>	High, favours evolocumab
Time horizon	The economic model was based on a 35 year time horizon. The nominated time horizon captured the majority of costs and benefits in patients with atherosclerotic disease.	Moderate favours evolocumab

Source: compiled during the evaluation

6.36 The Markov traces for mortality outcomes are summarised in the figure below. The Markov trace shows the impact of the mortality time lag with no difference between survival curves up to ■ years. After this point, the curves separate, with evolocumab treatment associated with substantial reductions in coronary death compared with both ezetimibe and placebo. The resubmission did not attempt to validate the model traces using data from other external sources.

Figure 1: Markov trace for CHD death (dashed line), other death (dotted line) and total death (full line)



Abbreviations: CHD, coronary heart disease

Note: The baseline age of patients was 64 years

Source: Figure 3.7.1 of the commentary; constructed during the evaluation using Evolocumab model v5_09a Excel model provided with the resubmission

6.37 The results of the modelled economic evaluation are summarised below. During the evaluation, additional steps were added to the economic analysis to explore the impact of modelled patient characteristics, distribution of cardiac events and time adjustments for cardiovascular risk and cardiovascular mortality (i.e. risk multipliers).

Table 8: Stepped economic evaluation of evolocumab versus ezetimibe or placebo in the treatment of non-familial hypercholesterolaemia with atherosclerotic disease

Type of resource item	Evolocumab	Ezetimibe	Placebo	Increment vs	
				Ezetimibe	Placebo
Step 1a: Trial-based LDL outcomes transformed to life years over a 2-year time horizon based on FOURIER patient populations. Included drug costs only. No discounting					
Costs	\$ [redacted]	\$ [redacted]	\$0	\$ [redacted]	\$ [redacted]
Life years	1.980	1.978	1.976	0.002	0.004
Incremental cost per life year gained				\$ [redacted]	\$ [redacted]
Step 1b: Modelled patient demographics (age 64 vs 62.5 years; proportion female 0.3 vs 0.246)					
Costs	\$ [redacted]	\$ [redacted]	\$0	\$ [redacted]	\$ [redacted]
Life years	1.978	1.976	1.974	0.002	0.004
Incremental cost per life year gained				\$ [redacted]	\$ [redacted]
Step 1c: Modelled baseline LDL (5.5 vs 2.53)					
Costs	\$ [redacted]	\$ [redacted]	\$0	\$ [redacted]	\$ [redacted]
Life years	1.981	1.977	1.974	0.004	0.007
Incremental cost per life year gained				\$ [redacted]	\$ [redacted]
Step 1d: Modelled CHD event rate (0.05 vs 0.042)					
Costs	\$ [redacted]	\$ [redacted]	\$0	\$ [redacted]	\$ [redacted]

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Type of resource item	Evolocumab	Ezetimibe	Placebo	Increment vs	
				Ezetimibe	Placebo
Life years	1.980	1.975	1.972	0.005	0.008
Incremental cost per life year gained				\$ [REDACTED]	\$ [REDACTED]
Step 1e: Modelled CHD event distribution (MI 37.8%; stroke 27.7%; CHD death 34.5% vs 62.0%; 23.5%; 14.5%)					
Costs	\$ [REDACTED]	\$ [REDACTED]	\$0	\$ [REDACTED]	\$ [REDACTED]
Life years	1.971	1.960	1.952	0.011	0.019
Incremental cost per life year gained				\$ [REDACTED]	\$ [REDACTED]
Step 2a: Modelled time horizon extrapolated to 35 years					
Costs	\$ [REDACTED]	\$ [REDACTED]	\$0	\$ [REDACTED]	\$ [REDACTED]
Life years	21.126	19.650	18.750	1.476	2.376
Incremental cost per life year gained				\$ [REDACTED]	\$ [REDACTED]
Step 2b: Include time adjustment for cardiovascular event rate (1.03 annual increase) and cardiovascular mortality (1.07 annual increase)					
Costs	\$ [REDACTED]	\$ [REDACTED]	\$0	\$ [REDACTED]	\$ [REDACTED]
LYs	19.468	17.310	16.126	2.157	3.341
Incremental cost per LY gained				\$ [REDACTED]	\$ [REDACTED]
Step 3: Introduce a time lag ([REDACTED] years) between LDL reduction and cardiovascular mortality benefit					
Costs	\$ [REDACTED]	\$ [REDACTED]	\$0	\$ [REDACTED]	\$ [REDACTED]
LYs	18.862	17.096	16.126	1.767	2.736
Incremental cost per LY gained				\$ [REDACTED]	\$ [REDACTED]
Step 4: Include additional costs associated with the management of cardiovascular events					
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Life years	18.862	17.096	16.126	1.767	2.736
Incremental cost per life year gained				\$ [REDACTED]	\$ [REDACTED]
Step 5: Include discount rate					
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Life years	11.617	10.919	10.521	0.698	1.096
Incremental cost per life year gained				\$ [REDACTED]	\$ [REDACTED]
Step 6: Transform outcomes to QALYs using the same utility score for each health state					
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	8.713	8.189	7.891	0.524	0.822
Incremental cost per QALY gained				\$ [REDACTED]	\$ [REDACTED]
Step 7: Apply disutility values for acute cardiovascular events					
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	8.681	8.137	7.825	0.544	0.856
Incremental cost per QALY gained				\$ [REDACTED]	\$ [REDACTED]
Step 8: Apply differential utility scores for each health state					
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	8.942	8.266	7.886	0.676	1.056
Incremental cost per QALY gained				\$ [REDACTED]	\$ [REDACTED]

Abbreviations: LDL, low density lipoprotein cholesterol; QALYs, quality-adjusted life years

Source: Table 3.8-2 (p 100) of the resubmission; 'Evolocumab Model v5.09a' Excel workbook

Note: The Fourier event rate (0.042 events per year) was based on a broader composite outcome (cardiovascular death, stroke and myocardial infarction) compared to the economic model (coronary death, ischaemic stroke and myocardial infarction) and therefore is likely to overestimate comparable event rates

6.38 Based on the economic model, treatment with evolocumab was associated with a cost per QALY gained of \$15,000 - \$45,000 compared to ezetimibe (replacement to ezetimibe) and \$15,000 - \$45,000 compared to placebo (add-on to existing therapies) in non-familial hypercholesterolaemia patients with atherosclerotic disease. The ESC noted that considerable uncertainty remained in terms of the model inputs and therefore in terms of the results provided. The key points of

uncertainty were baseline LDL (Step 1c above), coronary heart disease event distribution (Step 1e) and the time horizon (Step 2a).

6.39 The previous November 2017 submission estimated that treatment with evolocumab was associated with a cost per QALY gained of \$45,000 - \$75,000 compared to ezetimibe and \$15,000 - \$45,000 compared to placebo in non-familial hypercholesterolaemia patients with atherosclerotic disease. The difference in cost-effectiveness was primarily due to the lower effective price of evolocumab in the current resubmission.

6.40 The results of key sensitivity analyses are summarised below.

Table 9: Results of univariate sensitivity analyses

	Evolocumab versus ezetimibe			Evolocumab versus placebo		
	Incr cost	Incr QALY	ICER	Incr cost	Incr QALY	ICER
Base case	\$ [redacted]	0.676	\$ [redacted]	\$ [redacted]	1.056	\$ [redacted]
Time horizon (base case 35 years)						
15 years	\$ [redacted]	0.287	\$ [redacted]	\$ [redacted]	0.464	\$ [redacted]
25 years	\$ [redacted]	0.568	\$ [redacted]	\$ [redacted]	0.899	\$ [redacted]
Baseline LDL-cholesterol (base case 5.5 mmol/L)						
2.53 (FOURIER)	\$ [redacted]	0.366	\$ [redacted]	\$ [redacted]	0.546	\$ [redacted]
3.5	\$ [redacted]	0.481	\$ [redacted]	\$ [redacted]	0.728	\$ [redacted]
4.5	\$ [redacted]	0.586	\$ [redacted]	\$ [redacted]	0.900	\$ [redacted]
6.5	\$ [redacted]	0.752	\$ [redacted]	\$ [redacted]	1.196	\$ [redacted]
Event distribution (base case Heart Protection Study nonfatal MI 37.8%; nonfatal stroke 27.7%; CHD death 34.5%)						
Double fatal events in HPS (28.1%; 20.6%; 51.3%)	\$ [redacted]	0.726	\$ [redacted]	\$ [redacted]	1.124	\$ [redacted]
Halve fatal events in HPS (45.7%; 33.5%; 20.9%)	\$ [redacted]	0.604	\$ [redacted]	\$ [redacted]	0.952	\$ [redacted]
All nonfatal events MI (65.5%; 0%; 34.5%)	\$ [redacted]	0.588	\$ [redacted]	\$ [redacted]	0.925	\$ [redacted]
All nonfatal events stroke (0%; 65.5%; 34.5%)	\$ [redacted]	0.756	\$ [redacted]	\$ [redacted]	1.167	\$ [redacted]
FOURIER (62.0%; 23.5%; 14.5%) ^a	\$ [redacted]	0.508	\$ [redacted]	\$ [redacted]	0.810	\$ [redacted]
Cardiovascular mortality benefit time lag (base case [redacted] years)						
No lag	\$ [redacted]	0.848	\$ [redacted]	\$ [redacted]	1.326	\$ [redacted]
5 year lag	\$ [redacted]	0.613	\$ [redacted]	\$ [redacted]	0.958	\$ [redacted]
No mortality benefit	\$ [redacted]	0.142	\$ [redacted]	\$ [redacted]	0.232	\$ [redacted]
Persistence (base case: No discontinuations)						
0.5% discontinuations per month	\$ [redacted]	0.363	\$ [redacted]	\$ [redacted]	0.578	\$ [redacted]
1% discontinuations per month	\$ [redacted]	0.221	\$ [redacted]	\$ [redacted]	0.357	\$ [redacted]
2% discontinuations per month	\$ [redacted]	0.105	\$ [redacted]	\$ [redacted]	0.172	\$ [redacted]

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; ICER, incremental cost-effectiveness ratio; Incr, incremental; LDL-C, low density lipoprotein cholesterol; MI, myocardial infarction; QALY, quality-adjusted life year

Source: Table 3.9-1 (p 106-108) of the resubmission; 'Evolocumab Model v5.09a' Excel workbook

^a From Table 10-6, p129 FOURIER clinical study report. Summary of first component events of key secondary endpoint in placebo arm (cardiovascular death N=145; myocardial infarction N=618; stroke N=234; excludes patients with multiple events on the same day)

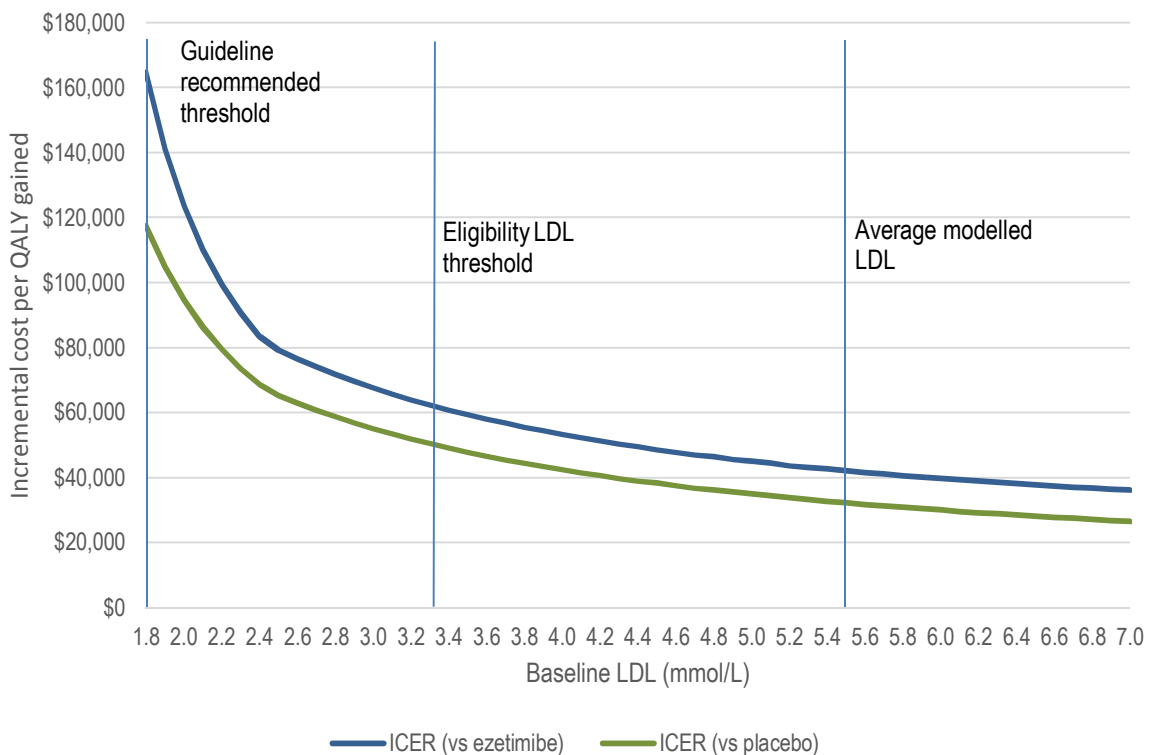
The redacted table shows ICERS in the range of \$15,000/QALY - \$75,000/QALY.

6.41 The results of the sensitivity analyses indicated that the model was most sensitive to time horizon, baseline LDL levels, distribution of cardiac events, cardiovascular mortality benefit and treatment persistence. The current model was more sensitive

to measures of persistence compared to the November 2017 model due to the introduction of a time lag between LDL reduction and cardiovascular mortality benefits.

- 6.42 The economic analyses were also sensitive to measures of compliance but these were inappropriately implemented as a flat reduction in drug costs. This was not reasonable, as non-compliance would affect both costs and health outcomes.
- 6.43 Given previous PBAC concerns regarding the definition of the target population, the estimated cost-effectiveness of evolocumab was plotted against changes in baseline LDL levels during the evaluation. These results should be interpreted with caution as they assume independence of baseline LDL levels and baseline cardiovascular risk.

Figure 2: Incremental cost per QALY gained over varying baseline LDL levels



Abbreviations: ICER, incremental cost effectiveness ratio; LDL, low density lipoprotein cholesterol; QALY, quality adjusted life year
 Source: constructed during the evaluation using Evolocumab model v5_09a Excel model provided with the resubmission

- 6.44 The estimated cost-effectiveness of evolocumab compared to ezetimibe and placebo was particularly sensitive to lower baseline LDL levels, which resulted in high cost-effectiveness ratios.

Drug cost/patient/year

- 6.45 The estimated drug cost for evolocumab per patient per year was \$ [REDACTED] (based on 13 scripts using the effective DPMQ \$ [REDACTED] for 2 x 140 mg fortnightly injection). The estimated drug cost for evolocumab per patient per year was \$ [REDACTED] in the previous November 2017 submission (based on 13 scripts using the effective DPMQ \$ [REDACTED] for 2 x 140 mg fortnightly injection).
- 6.46 The estimated drug cost for ezetimibe per patient per year was \$802 (based on 12 scripts, using the current DPMQ \$66.84 for ezetimibe 30 x 10 mg tablets).

Estimated PBS usage & financial implications

- 6.47 This resubmission was not considered by DUSC. The resubmission used a market share approach to estimate the utilisation/financial implications associated with the PBS listing of evolocumab for non-familial hypercholesterolaemia with atherosclerotic disease.
- 6.48 Key changes to the budget impact estimates included a reduction in the proposed effective price for evolocumab, estimates of patients with atherosclerotic disease no longer differentiate between familial and non-familial hypercholesterolaemia and an update of estimates from 2018-2023 to 2019-2024.

Table 10: Estimated utilisation and cost to the PBS in the first six years of listing for non-familial atherosclerotic cardiovascular disease

	Year 1 (2019)	Year 2 (2020)	Year 3 (2021)	Year 4 (2022)	Year 5 (2023)	Year 6 (2024)
PBS/RPBS market for ASCVD patients with LDL > 3.3 mmol/L	██████	██████	██████	██████	██████	██████
Evolocumab uptake	25%	40%	50%	60%	60%	60%
Evolocumab patients	██████	██████	██████	██████	██████	██████
Patients using fortnightly dosing (80%)	██████	██████	██████	██████	██████	██████
Evolocumab 140 mg fortnightly scripts (11.05 scripts per patient)	██████	██████	██████	██████	██████	██████
Patients using monthly dosing (20%)	██████	██████	██████	██████	██████	██████
Evolocumab 420 mg monthly scripts (10.2 scripts per patient)	██████	██████	██████	██████	██████	██████
Total cost of evolocumab (effective DPMQ)	\$██████	\$██████	\$██████	\$██████	\$██████	\$██████
Patient co-payments (\$13.93 per script)	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████
Total cost less co-payment	\$██████	\$██████	\$██████	\$██████	\$██████	\$██████
Change in use of statins and ezetimibe	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████
Net cost to PBS/RPBS	\$██████	\$██████	\$██████	\$██████	\$██████	\$██████

Abbreviations: FH, familial hypercholesterolaemia; ASCVD, atherosclerotic cardiovascular disease; DPMQ, dispensed price for maximum quantity; Q2W, once every 2 weeks; QM, once monthly.

Source: Table 4.2-2 (p 119), Table 4.2-3 (p 119), Table 4.2-4 (p 119), Table 4.2-5 (p 120), Table 4.2-6 (p 120), Table 4.2-7 (p 120), Table 4.2-8 (p 121), Table 4.3-1 (p 122), Table 4.4-1 (p 122), Table 4.4-2 (p 122) of the resubmission

The redacted table shows that at Year 6, the estimated number of patients was 50,000 – 100,000.

6.49 The net cost of listing evolocumab for the treatment of patients with non-familial hypercholesterolaemia with atherosclerotic cardiovascular disease was estimated to be up to more than \$100 million in the sixth year of listing (published price more than \$100 million). The estimated cumulative net cost over six years was more than \$100 million (published price more than \$100 million). The PSCR clarified that there is an approximately 5% overlap in estimated total cost with the familial hypercholesterolaemia population which received a positive recommendation at the March 2018 PBAC meeting. Removing this overlap, the estimated total net cost to the PBS/RPBS would be reduced by between less than \$10 million in year 1 and up to \$10 - \$20 million in year 6.

6.50 The PBAC noted that significant cost-offsets were attributed to reduced use of statins and ezetimibe.

6.51 The previous November 2017 submission estimated that listing evolocumab for non-familial hypercholesterolaemia with atherosclerotic cardiovascular disease would be

associated with a cumulative cost of more than \$100 million over six years based on the effective price. The difference in budget impact implications was primarily due to the lower effective price of evolocumab in the current resubmission.

- 6.52 The estimated utilisation of evolocumab on the PBS remains uncertain as a number of concerns previously raised by DUSC still apply to the revised estimates (difficulty in estimating size of population meeting eligibility criteria, uncertain market growth rates, uncertain uptakes rates and the assumption that the only non-statin therapy replaced is ezetimibe).

Quality Use of Medicines

- 6.53 The resubmission claimed that the requested Authority Required restriction and the amendments to the proposed restriction defining maximum tolerated statin dose would reduce the risk of inappropriate use.
- 6.54 The resubmission repeated the previous request for a stakeholder meeting to establish the appropriate clinical position for PCSK9 inhibitors in relation to existing lipid lowering therapies subsidised under the PBS. The resubmission suggested that it may be prudent to consider the intent and cost-effective use of all lipid lowering medicines on the PBS.
- 6.55 The resubmission also stated that the sponsor provides a number of education tools for clinicians to assist in identifying eligible patients and provides financial support for the maintenance of a national familial hypercholesterolaemia registry. A patient support program for evolocumab was also commenced in 2016 and includes information about evolocumab and an injection reminder service.

Financial Management – Risk Sharing Arrangements

- 6.56 The resubmission proposed a tiered risk share arrangement to address the uncertainty associated with the estimated extent of use. The resubmission argued that a partial rebate for Tier 2 and a full rebate for Tier 3 is a reasonable compromise as it accommodates both the uncertainty in the estimates of the eligible population as well potential benefit these patients will derive from evolocumab treatment.

Table 11: Proposed tiered financial caps – Commonwealth Payment

Net cost to PBS	Year 1 (2019)	Year 2 (2020)	Year 3 (2021)	Year 4 (2022)	Year 5 (2023)	Year 6 (2024)
Tier 1	No additional rebate					
Tier 1 Cap (based on government expenditure)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Tier 2	[REDACTED] % additional rebate					
Tier 2 Cap (based on government expenditure + [REDACTED]%)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Tier 3	[REDACTED] % additional rebate					

Source: Table ES.9 (p 26) of the resubmission

- 6.57 A similar risk share arrangement was also proposed in the March 2018 minor submission for high-risk heterozygous familial hypercholesterolaemia. In regards to this previous proposal, the PBAC raised concerns regarding the cap (estimated government expenditure + █%) and rebate (additional █% rebate) for Tier 2 which were considered somewhat arbitrary and required further revision [5.7 March 2018 evolocumab Public Summary Document].

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of evolocumab for patients with non-familial hypercholesterolaemia (non-FH) with atherosclerotic cardiovascular disease (ASCVD) on the basis of an inadequately defined patient population, an uncertain incremental cost-effectiveness ratio (ICER) and high and uncertain patient population numbers.
- 7.2 The PBAC again acknowledged that there is a high and unmet clinical need for patients with non-FH and ASCVD who are not adequately controlled or intolerant to available lipid-lowering therapies, but considered that the population subgroups that would most benefit from treatment remained inadequately defined. The PBAC recalled that it had previously been reluctant to consent to a stakeholder meeting to discuss the role of PCSK9 inhibitors without greater clarity and agreement about the non-FH population who would most benefit from treatment and further economic modelling of the cost-effectiveness and opportunity cost of a broader listing. The PBAC also stated that outcome data for alirocumab would be needed to inform such discussion. However, following the publication of preliminary alirocumab data (from the ODYSSEY OUTCOMES trial) and the failure of the sponsor of evolocumab to provide an adequately defined population, the PBAC considered that a stakeholder meeting was required.
- 7.3 The PBAC considered that LDL-c 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-c, multiple previous cardiovascular events, multi-vessel coronary artery disease, etc, to allow the determination of a cost effective population.
- 7.4 The resubmission nominated both ezetimibe and placebo as the main comparators. The PBAC considered that these comparators were appropriate for the combined familial and non-familial hypercholesterolaemia submission in November 2017. However, for non-FH alone the PBAC were concerned that by nominating ezetimibe as a comparator, it would be replaced in the treatment algorithm by evolocumab.
- 7.5 The PBAC considered that for those 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. Further, the LDL-c

threshold of 3.3mmol/L was considered arbitrary in the context of secondary prevention in the population with non-FH with ASCVD.

- 7.6 The PBAC noted that the resubmission included more conservative assumptions about the time to cardiovascular mortality benefit in the form of a [REDACTED] year time lag between LDL reduction and impact on cardiovascular death, as per the familial hypercholesterolaemia minor submission in March 2018. The PBAC considered that while there is a biological plausibility of a reduction in CV mortality, there was no direct data to support the length of the time lag or the magnitude of the reduction in cardiovascular mortality in secondary prevention of CAD. The PBAC noted that this was a key driver of the economic model.
- 7.7 The PBAC again noted that the FOURIER trial population was more aligned with the non-FH with ASCVD population and reiterated its previous recommendation that these trial data could be used to better inform the economic model. 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. The PBAC also considered that cost offsets related to ezetimibe use be reassessed given evolocumab should be used after, rather than substitute for, ezetimibe.
- 7.8 The PBAC noted the proposed price reduction and risk share arrangements proposed in the resubmission, but considered that the financial impact of listing evolocumab in patients with non-FH remained 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.
- 7.9 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

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

The sponsor had no comment.