5.09 EVOLOCUMAB
140 mg pre-filled injection pen;
Repatha®, Amgen Pty Ltd.

1 Purpose of Application

1.1 The submission sought to open a dialogue regarding the potential future listing of evolocumab on the PBS for the treatment of hypercholesterolaemia.

2 Requested listing

2.1 The requested listing is outlined below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
EVOLOCUMAB				Repatha® Amgen Pty Ltd
140 mg/mL injection, Sureclick refilled syringe, 1 x 1 mL	2	5	$[redacted]	
140 mg/mL injection, Sureclick refilled syringe, 1 x 1 mL	3	5	$[redacted]	

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition:	Hypercholesterolaemia
PBS Indication:	Hypercholesterolaemia
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☒ Authority Required - Telephone ☒ Authority Required – Emergency ☒ Authority Required - Electronic ☐ Streamlined

Clinical criteria:	The treatment must be in conjunction with dietary therapy and exercise, AND Patient must have cholesterol levels that are inadequately controlled with an HMG CoA reductase inhibitor (statin); OR Patient must have developed a clinically important product-related adverse event during treatment with a statin necessitating a reduction in the statin dose; OR Patient must have a contraindication to treatment with a statin, AND Patient must have coronary heart disease; OR Patient must have peripheral vascular disease; OR Patient must have symptomatic cerebrovascular disease; OR Patient must have heterozygous familial hypercholesterolaemia; OR Patient must have a family history of coronary heart disease; OR Patient must have diabetes mellitus; OR Patient must have hypertension. ~~an Aboriginal or Torres Strait Islander person.~~
Prescriber Instructions	Inadequate control with a statin is defined as follows: (1) where the patient falls into a category for which the General Statement for Lipid-Lowering Drugs includes an initial cholesterol threshold for PBS-subsidy (i.e. a patient not in a very high risk category), a cholesterol level in excess of that threshold after at least 3 months of treatment at a maximum tolerated dose of a statin, in conjunction with dietary therapy and exercise. The dose and duration of statin treatment and the cholesterol level which shows inadequate control must be documented in the patient's medical records when evolocumab is initiated. The cholesterol level which shows inadequate control must be no more than 2 months old when evolocumab is initiated; or (2) where the patient falls into a category for which the General Statement for Lipid-Lowering Drugs allows PBS-subsidised treatment with a statin at any cholesterol level (i.e. a very high risk category patient), a cholesterol level in excess of 4 mmol per L after at least 3 months of treatment at a maximum tolerated dose of a statin, in conjunction with dietary therapy and exercise. The dose and duration of statin treatment and the cholesterol level which shows inadequate control must be documented in the patient's medical records when evolocumab is initiated. The cholesterol level which shows inadequate control must be no more than 2 months old when evolocumab is initiated. 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, persistence elevations of serum transaminases (greater than 3 times the upper limit of normal) during treatment with a statin.

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition:	Hypercholesterolaemia
PBS Indication:	Hypercholesterolaemia
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☒ Authority Required - Telephone ☒ Authority Required – Emergency ☒ Authority Required - Electronic ☐ Streamlined
Clinical criteria:	Patient must have homozygous familial hypercholesterolaemia, AND Patient must be eligible for PBS-subsidised lipid-lowering medication (according to the criteria set out in the General Statement for Lipid-Lowering Drugs).

2.2 Listing was requested on a cost-effectiveness basis compared to ezetimibe and placebo.

2.3 The submission proposed that patients with familial hypercholesterolaemia (both heterozygous and homozygous) should be re-classified as very-high cardiovascular risk under the PBS general statement for lipid-lowering drugs therefore auto-qualifying for statin therapy and requiring a less stringent target for subsequent line therapy with evolocumab and/or ezetimibe. No clinical data were provided to support the requested change.

2.4 The submission proposed a more restrictive listing for evolocumab compared to ezetimibe, which was poorly justified and may be difficult to administer in clinical practice.

2.5 The appropriateness of a streamlined authority listing is unclear given that evolocumab is a first-in-class medication with substantial drug costs and potential for use outside the requested restriction.

3 Background

3.1 Evolocumab was lodged under the TGA-PBAC parallel process (regulatory decision due in late 2015). No TGA documentation was available during the evaluation or at the time of PBAC consideration.

3.2 The PBAC has not previously considered evolocumab.

4 Clinical place for the proposed therapy

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 submission positioned evolocumab as an alternative to ezetimibe in patients contraindicated/intolerant to statins and patients failing to achieve target lipid levels with statins alone. The submission also proposed that evolocumab may be used in addition to statins and ezetimibe for patients with familial hypercholesterolaemia (both heterozygous and homozygous). The submission did not address the potential for evolocumab to be used as an add-on therapy for non-familial hypercholesterolaemia. The ESC considered that it was too early to make a judgement on the clinical place in therapy given that relevant TGA documents were not available. The ESC stated that it was unclear at this stage on how evolocumab would actually be used in practice.

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

5 Comparator

5.1 Ezetimibe and placebo. The evaluation noted that these were appropriate comparators.

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 (15), health care professionals (2), and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with evolocumab including improvement in quality of life, high effectiveness of lowering LDL cholesterol, and reducing the risk of heart disease and stroke.

6.3 The PBAC noted the advice received from FH Family Support Group of Western Australia clarifying the likely use of evolocumab in clinical practice.

Clinical trials

6.4 The submission was based on a series of head-to-head comparisons between evolocumab and the nominated comparators with additional long-term supportive studies.

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

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
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 hypercholesterolemia: 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 Hypercholesterolemia 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 hypercholesterolemia: The LAPLACE-2 randomized clinical trial	JAMA 311: 1870–1882
	Robinson JG et al (2014). 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 hypercholesterolemia on background statin therapy	Clinical Cardiology 37: 195–203
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
	Cho L et al (2014). 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 hypercholesterolemia who are intolerant of statin therapy	Clinical Cardiology 37: 131–139
	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 hypercholesterolemia.	Internal study report
	Ral F et al (2014). PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial.	Lancet (early online publication) doi:10.1016/S0140-6736(14)61399-4
20110233 (TESLA)	Amgen Clinical Study Report (2014). A 2-part, Phase 2/3 Study to Assess the Safety, Tolerability and Efficacy of AMG 145 in Subjects With Homozygous Familial Hypercholesterolemia. Part A – Open-label, Single-arm,	Internal study report

Trial ID	Protocol title/ Publication title	Publication citation
	Multicenter Pilot Study to Evaluate Safety, Tolerability and Efficacy of AMG 145 in Subjects With Homozygous Familial Hypercholesterolemia. Part B – Double-blind, Randomised, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of AMG 145 in Subjects With Homozygous Familial Hypercholesterolemia	
	Raal F et al (2014). Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial.	Lancet (early online publication) doi:10.1016/S0140-6736(14)61374-X
	Stein EA et al (2013). Effect of the proprotein convertase subtilisin/kexin 9 monoclonal antibody, AMG 145, in homozygous familial hypercholesterolemia	Circulation 128: 2113–2120
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 370:1809-19.
Supportive studies		
20110110 (OSLER-1)	Amgen Clinical Study Report (2014). A Multicenter, Controlled, Open-label Extension Study to Assess the Long-term Safety and Efficacy of Evolocumab.	Internal study report [Interim July 2014]
	Koren M et al (2014). Efficacy and safety of longer-term administration of evolocumab (AMG 145) in patients with hypercholesterolemia: 52-week results from the open-label study of long-term evaluation against LDL-C (OSLER) randomized trial	Circulation 129: 234–243
20110271 (TAUSSIG)	Amgen Clinical Study Report (2014). A Multicenter, Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of AMG 145 on LDL-C in Subjects With Severe Familial Hypercholesterolemia	Internal study report [Interim July 2014]
20120138 (OSLER-2)	Amgen Clinical Study Report (2014). A Multicenter, Controlled, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 145 (Interim Clinical Study Report) - OSLER-2	Internal study report [Interim July 2014]

A clinical outcomes study comparing evolocumab with placebo as an adjunct to standard care in patients with cardiovascular disease and primary hyperlipidaemia or mixed dyslipidaemia is due to report in 2018 (FOURIER).

6.6 The key features of the direct randomised trials are summarised in the table below.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome	Use in modelled evaluation
Evolocumab vs ezetimibe or placebo						
GAUSS-2	307	MC, R, DB, PG, AC 4 treatment arms 12 weeks	Low	Patients[a] who are statin intolerant	Change in LDL levels	Baseline risk, LDL levels
LAPLACE-2	2,067	MC R, DB, PG, AC, PC 24 treatment arms 12 weeks	Low	Patients[a] requiring combination with statin	Change in LDL levels	Baseline risk, LDL levels
MENDEL-2	615	MC, R, DB, PG, AC, PC 6 treatments arms 12 weeks	Low	Low-risk patients[a] requiring monotherapy	Change in LDL levels	Not used
RUTHERFORD-2	331	MC, R, DB, PG, PC 4 treatment arms 12 weeks	Low	HeFH	Change in LDL levels	Baseline risk, LDL levels
TESLA	50	MC, R, DB, PG, PC 4 treatment arms 12 weeks	Low	HoFH	Change in LDL levels	Not used
DESCARTES	905	MC, R, DB, PG, PC 4 treatment arms 52 weeks	Low	Patients[a] failing current therapies	Change in LDL levels	Not used

Abbreviations: AC, active-control; DB, double blind; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; LDL, low-density lipoprotein; MC, multicentre; PC, placebo-control; PG, parallel-group; R, randomised.

Source: Constructed during the evaluation

[a] Patients with primary hyperlipidaemia (non-familial and heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia

The included trials appear to have limited applicability to the requested PBS population in terms of baseline risk.

Comparative effectiveness

6.7 The main outcome of the submission was mean change in LDL levels from baseline with evolocumab, ezetimibe and placebo. The ESC noted the submission's reliance on surrogates to predict extent of change in final outcomes and raised concerns on the use of LDL levels as surrogate measures. Further, the submission presented its claim of comparative effectiveness under the assumption that the lower the LDL level, the more effective evolocumab is in treatment. However, given that evolocumab acts on receptors which will continue to reduce LDL levels, the ESC raised concerns on whether an essential level of LDL is required in the human body.

Mean percent change in calculated LDL levels in patients with primary hyperlipidaemia and mixed dyslipidaemia

Trial	Evolocumab, Mean (95% CI)	Ezetimibe, Mean (95% CI)	Placebo, Mean (95% CI)	Treatment difference, Mean (95% CI)
Fortnightly dosing, Baseline to Week 10/12				
GAUSS-2 (intolerant to statins)	-57.1% (-60.8, -53.4)	-19.0% (-23.9, -14.1)	-	vs. ezetimibe: -38.1% (-43.6, -32.6)
LAPLACE-2 (low dose statin)	-64.1% (-67.5, -60.8)	-23.4% (-28.3, -18.5)	8.5% (3.9, 13.2)	vs. ezetimibe: -40.8% (-46.6, -34.9) vs. placebo: -72.7% (-78.4, -66.9)
LAPLACE-2 (high dose statin)	-65.3% (-71.0, -59.5)	-17.3% (-25.3, -9.3)	12.8% (4.5, 21.1)	vs. ezetimibe: -48.0% (-57.8, -38.1) vs. placebo: -78.1% (-88.1, -68.0)
MENDEL-2 (monotherapy, low risk)	-57.8% (-59.9, -55.6)	-17.6% (-20.5, -14.6)	-0.3% (-3.3, 2.6)	vs. ezetimibe: -40.2% (-43.8, -36.6) vs. placebo: -57.4% (-61.0, -53.9)
RUTHERFORD-2 (HeFH)	-62.7% (-66.2, -59.2)	-	-1.4% (-6.3, 3.6)	vs. placebo: -61.3% (-67.2, -55.4)
Monthly dosing, Baseline to Week 10/12				
GAUSS-2 (intolerant to statins)	-55.8% (-58.9, -52.8)	-16.6% (-20.7, -12.5)	-	vs. ezetimibe: -39.2% (-43.7, -34.8)
LAPLACE-2 (low dose statin)	-64.1% (-67.7, -60.4)	-18.8% (-24.0, -13.6)	0.4% (-4.8, 5.7)	vs. ezetimibe: -43.2% (-51.6, -38.9) vs. placebo: -64.5% (-70.9, -58.1)
LAPLACE-2 (high dose statin)	-68.1% (-72.9, -63.2)	-22.1% (-29.0, -15.2)	9.9% (3.1, 16.7)	vs. ezetimibe: -46.0% (-54.4, -37.5) vs. placebo: -78.0% (-86.3, -69.6)
MENDEL-2 (monotherapy, low risk)	-59.8% (-61.9, -57.7)	-19.1% (-22.0, -16.2)	-0.1% (-3.0, 2.8)	vs. ezetimibe: -40.7% (-44.1, -37.3) vs. placebo: -59.7% (-63.1, -56.2)
RUTHERFORD-2 (HeFH)	-64.7% (-68.1, -61.4)	-	1.5% (-3.2, 6.2)	vs. placebo: -66.2% (-71.9, -60.6)
Monthly dosing, Baseline to Week 52				
DESCARTES (various background therapies)	-50.6% (-53.2, -48.0)	-	8.7% (5.1, 12.4)	vs placebo: -59.3% (-63.8, -54.9)

Abbreviations: CI, confidence interval; HeFH, heterozygous familial hypercholesterolaemia; LDL, low-density lipoprotein; SD, standard deviation

Treatment with evolocumab (fortnightly and monthly dosing) was associated with statistically significant decreases in calculated LDL levels compared to ezetimibe (approximately 40% reduction) and placebo (approximately 60-70% reduction) in patients with primary hyperlipidaemia and mixed dyslipidaemia. Subgroup/sensitivity analyses indicated that results were broadly consistent using different LDL assessment methods, different background therapies, different administration protocols and across different patient subgroups.

Mean percent change in calculated LDL levels in patients with homozygous familial hypercholesterolaemia

Trial	Evolocumab, Mean (95% CI)	Placebo, Mean (95% CI)	Treatment difference, Mean (95% CI)
Monthly dosing, Baseline to Week 12			
TESLA (HoFH)	-23.1% (-30.8, -15.4)	9.0% (-1.5, 19.6)	vs. placebo: -32.1% (-45.1, -19.2)
- LDLR defective subgroup	-29.3% (-36.2, -22.4)	12.0% (1.5, 22.4)	vs. placebo: -41.3% (-53.8, -28.7)
- LDLR non-defective subgroup	-12.5% (-29.5, 4.5)	7.0% (-13.8, 27.7)	vs. placebo: -19.5% (-45.4, 6.5)

Abbreviations: CI, confidence interval; HoFH, homozygous familial hypercholesterolaemia; LDL, low-density lipoprotein; LDLR, low density lipoprotein receptor; RCT, randomised controlled trial; SD, standard deviation

Treatment with monthly evolocumab was associated with statistically significant decreases in calculated LDL levels compared to placebo (approximately 30% reduction) in the overall trial population of homozygous familial hypercholesterolaemia patients. Subgroup analyses suggested that low-density lipoprotein receptor (LDLR) status may be a treatment effect modifier with evolocumab showing greater reduction in patients who are LDLR defective versus patients who are LDLR non-defective.

The current published literature supports the hypothesis that a reduction in LDL levels is associated with a reduction in cardiovascular risk. Therefore the greater LDL reductions associated with evolocumab treatment compared to ezetimibe and placebo may translate into meaningful reductions in cardiovascular events. However, the magnitude of benefit remains unclear as there are specific issues with LDL hypothesis which may affect the application of these findings to the evolocumab trial results:

- Whether it is reasonable to extrapolate further clinical benefit beyond the range of absolute changes reported in the CTTC analysis (approximately 0-2 mmol/L)? How much cardiovascular risk is actually modifiable through reductions in LDL levels?
- Whether it is reasonable to extrapolate further clinical benefits from achieving endpoint LDL levels lower than those reported in the CTTC analysis (approximately 1.5-3 mmol/L) and IMPROVE-IT trial (approximately 1.3 mmol/L)? At what point does the reduction in LDL levels switch from beneficial to being harmful?
- Is the quantitative relationship between LDL reduction and cardiovascular outcomes the same for all treatments or are there relevant differences due to other treatment effects?
- Is the quantitative relationship between LDL reduction and cardiovascular outcomes the same for all patient populations (particularly between non-familial, heterozygous familial and homozygous familial hypercholesterolaemia)?

Comparative harms

6.8 The incidence of adverse events was highly variable between trials and did not consistently favour evolocumab, ezetimibe or placebo. There was no apparent difference in the incidence of adverse events with either fortnightly or monthly dosing of evolocumab.

6.9 The most frequently reported adverse events 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).

6.10 Regulatory bodies have not yet assessed the safety of evolocumab. There is limited adverse event data (both in terms of number of patients treated and duration of therapy) available for evolocumab treatment. The ESC raised concerns of the potential higher risk of infections, particularly in a subpopulation already using another monoclonal antibody for a different disease. The co-administration of monoclonal antibodies has not been observed and the long-term adverse events in the requested population are unknown.

Benefits/harms

6.11 On the basis of direct evidence presented by the submission, the comparison of evolocumab (fortnightly) and ezetimibe in patients with primary hyperlipidaemia and mixed dyslipidaemia resulted in:

- approximately a 40% relative reduction in LDL levels over a 12-week treatment duration
- no apparent difference in adverse events over a 12-week treatment duration.

6.12 On the basis of direct evidence presented by the submission, the comparison of evolocumab (fortnightly) and placebo in patients with primary hyperlipidaemia and mixed dyslipidaemia resulted in:

- approximately a 60-70% relative reduction in LDL levels over a 12-week treatment duration
- no apparent difference in adverse events over a 12-week treatment duration.

6.13 On the basis of direct evidence presented by the submission, the comparison of evolocumab (monthly) and ezetimibe in patients with primary hyperlipidaemia and mixed dyslipidaemia resulted in:

- approximately a 40% relative reduction in LDL levels over a 12-week treatment duration
- no apparent difference in adverse events over a 12-week treatment duration.

6.14 On the basis of direct evidence presented by the submission, the comparison of evolocumab (monthly) and placebo in patients with primary hyperlipidaemia and mixed dyslipidaemia resulted in:

- approximately a 60-70% relative reduction in LDL levels over a 12-52 week treatment duration
- no apparent difference in adverse events over a 12-52 week treatment duration.

6.15 On the basis of direct evidence presented by the submission, the comparison of evolocumab (monthly) and placebo in patients with homozygous familial hypercholesterolaemia resulted in:

- approximately a 30% relative reduction in LDL levels over a 12-week treatment duration.

- no apparent difference in adverse events over a 12-week treatment duration.

Clinical claim

6.16 The submission described evolocumab as superior in terms of efficacy and similar in terms of safety compared to ezetimibe and placebo. The ESC noted that this claim is based on LDL levels as a surrogate measure. The ESC further noted that there was limited information available with regards to safety of evolocumab and therefore considered that the clinical claim is inadequately supported.

6.17 The PBAC did not comment further on the clinical claim because the efficacy and safety of evolocumab had not been considered by the TGA delegate before the time of PBAC consideration, and no evaluation documents from the TGA were available.

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

Economic analysis

6.18 The submission presented a modelled economic analysis assessing the cost-effectiveness of fortnightly evolocumab when used as a replacement or as an add-on therapy (heterozygous familial hypercholesterolaemia only) to ezetimibe in patients with primary hyperlipidaemia and mixed dyslipidaemia. No economic evaluation was presented for monthly evolocumab as the submission did not request listing of this dosing regimen for this patient population. The ESC noted that one of the main issues in the economic model is determining the treatment population.

6.19 No economic evaluation was presented for the use of evolocumab in patients with homozygous familial hypercholesterolaemia or for the use of evolocumab as an add-on therapy in patients with non-familial hypercholesterolaemia.

Summary of model structure and rationale

Component	Summary
Time horizon	35 years in the model base case versus 12 weeks in trials
Outcomes	% reduction in LDL; LYs; QALYs
Methods used to generate results	Markov cohort expected value analysis
Health states	Primary prevention setting (no CHD); secondary prevention following a non-fatal myocardial infarction; secondary prevention following a stroke; or dead
Cycle length	Monthly
Transition probabilities	Framingham risk equations; adjusted for treatment-related reduction in LDL and prior events
Discount rate	5% for costs and outcomes
Software package	Excel 2010

Abbreviations: CHD, coronary heart disease; LDL, low-density lipoprotein; LYs, life years; QALY, quality adjusted life year
Source: Constructed during the evaluation

6.20 Key issues with the economic model are summarised in the table below.

6.21 Overall, the ESC noted that the model was driven by three main steps:
a. estimate baseline CHD risks from the Framingham Risk Equations
b. adjust baseline CHD risks by applying a risk (multiplicative) multiplier for familial hypercholesterolaemia to those patients with a family history of premature CHD, and a separate risk (multiplicative) multiplier for those patients with prior MI or

stroke before and during the model. No further adjustments were made to account for the fact that, by definition, some of the remaining subgroups would have had a lower risk

c. apply the derived relative risk reduction for evolocumab and its comparators to the adjusted baseline CVD risks.

Key issues with the model

Description	Method/Value	Impact
Baseline cardiovascular risk	Patient characteristics of the trial populations (with limited applicability to the proposed PBS population) were converted to cardiovascular risk using the Framingham risk equation (risk calculator was not applied to the data appropriately). Post-hoc subgroup analyses were based on poorly justified threshold cholesterol levels. Additional analyses assumed all patients had coronary heart disease, diabetes or hypertension (which is inappropriate as other baseline characteristics are not independent variables). The risk multiplier for familial hypercholesterolaemia (RR=4) was applied to patients with a family history of premature CHD (in some of the base cases, all patients were assumed to have familial hypercholesterolaemia or family history of premature CHD). The RR of 4 was derived from comparing the familial hypercholesterolaemia population with the general population, and was inappropriately applied to the risk estimates for the trial populations of patients with hypercholesterolaemia, thus over-estimating the risk multiplier effect. Additional risk multipliers for prior events were estimated using primary and secondary prevention risk calculations models (models were not applied to the data appropriately). A multiplicative effect with familial hypercholesterolaemia was assumed for patients with prior MI or stroke (RR=4x7=28).	High
Transformation of LDL outcomes to cardiovascular outcomes	The relative change in LDL level for evolocumab and each of its comparators was converted to an absolute change based on the baseline value reported in the trial population (with limited applicability to the proposed PBS population), with additional post-hoc subgroup analyses based on poorly justified threshold cholesterol levels. The absolute change in LDL was then converted to a relative risk reduction in cardiovascular outcomes for evolocumab or ezetimibe compared to placebo based on the results of the CTTC statin meta-analysis. This transformation required extrapolation of the CTTC analysis beyond the bounds of the published analyses (unclear whether this is reasonable).	High
Treatment adherence	The 35-year model assumes all patients remain on treatment until death, with a constant and continuing treatment effect. The ongoing treatment effect is based on observed effect **over the duration** of 12 week trial; whereas the estimate of ongoing costs is based on the 95% of patients on treatment who remained adherent **at the end** of 12 week trial	High

Source: Constructed during the evaluation

6.22 The results of the economic model are summarised below.

Results of the modelled economic evaluation

Step/Analysis	Incremental cost vs. EZE/PBO	Increment QALYs vs. EZE/PBO	Cost per QALY
Step 2 (35 year time horizon)			
GAUSS-2	$ [redacted]	[redacted]	$ [redacted]
LAPLACE-2	$ [redacted]	[redacted]	$ [redacted]
RUTHERFORD-2	$ [redacted]	[redacted]	$ [redacted]
Step 3 (higher-risk populations)			
GAUSS-2 POPULATIONS			
G-3.3	$ [redacted]	[redacted]	$ [redacted]
G-CHD-3.3	$ [redacted]	[redacted]	$ [redacted]
G-DM-3.3	$ [redacted]	[redacted]	$ [redacted]
G-5.5	$ [redacted]	[redacted]	$ [redacted]
G-DM-5.5	$ [redacted]	[redacted]	$ [redacted]
G-HC	$ [redacted]	[redacted]	$ [redacted]
G-HT-HC	$ [redacted]	[redacted]	$ [redacted]
LAPLACE-2 POPULATIONS			
L-3.3	$ [redacted]	[redacted]	$ [redacted]
L-CHD-3.3	$ [redacted]	[redacted]	$ [redacted]
L-DM-3.3	$ [redacted]	[redacted]	$ [redacted]
L-5.5	$ [redacted]	[redacted]	$ [redacted]
L-DM-5.5	$ [redacted]	[redacted]	$ [redacted]
L-HC	$ [redacted]	[redacted]	$ [redacted]
L-HT-HC	$ [redacted]	[redacted]	$ [redacted]
RUTHERFORD-2 POPULATIONS			
R-vsEze	$ [redacted]	[redacted]	$ [redacted]
R-3.3-vsPla	$ [redacted]	[redacted]	$ [redacted]
R-3.3-vsEze	$ [redacted]	[redacted]	$ [redacted]
R-HC-vsPla	$ [redacted]	[redacted]	$ [redacted]
R-HC-vsEze	$ [redacted]	[redacted]	$ [redacted]

Abbreviations: CHD, coronary heart disease; DM, diabetes mellitus; EVO, evolocumab; EZE, ezetimibe; HC, high cholesterol; HT, hypertension; LYs, life years; PBO, placebo; QALYs, quality-adjusted life years

Note: Nominated subgroup thresholds were: LDL ≥ 3.3 mmol/L based on proposed threshold for very-high risk patients; TC ≥ 5.5 mmol/L based on current threshold for lower risk diabetes patients; LDL-C > 5 mmol/L OR TC > 6.5 mmol/L OR TC > 5.5 mmol/L and HDL < 1 mmol/L based on current threshold for lower risk patients with familial hypercholesterolaemia/family history of cardiovascular disease

6.23 Based on the economic model, treatment with evolocumab was associated with costs per QALY gained ranging from $45,000 - $75,000 to $105,000 - $200,000 against ezetimibe and $45,000/QALY – $75,000/QALY to $45,000/QALY – $75,000/QALY against placebo (when used as add-on therapy for patients with heterozygous familial hypercholesterolaemia). The ESC advised that these estimates should not be considered reliable given major concerns regarding the calculation of baseline risk, implementation of treatment adherence and the general uncertainty associated with the transformation of LDL levels to cardiovascular outcomes.

6.24 The results of the sensitivity analyses conducted during the evaluation indicate that evolocumab is unlikely to be considered cost-effective in patients with non-familial hypercholesterolaemia (cost per QALY gained ranging from $75,000/QALY – $105,000/QALY, $105,000/QALY – $200,000/QALY or more than $200,000/QALY versus ezetimibe). Based on utilisation estimates presented in the submission this population represents approximately 90% of requested PBS population.

6.25 The ESC noted several issues with the economic model and suggested changes which are detailed in the table below.

Changes to the submitted economic model suggested by the ESC

	Issue	Action
1	Define a representative PBS population.	Systolic blood pressure, total cholesterol, HDL and smoking status could all be derived from age- and gender-stratified populations from the National Health Survey (NHS). The risk factor combinations could be based on NHS conditional prevalence data. Adjustments also may be appropriate for the sub-population of patients who are contraindicated/ intolerant to statins and the sub-population of patients who fail to achieve target lipid levels with statins alone.
2	Combined application of original, and primary and secondary Framingham risk equations.	Primary and secondary Framingham risk equations could be used directly, rather than applying ratios derived from the primary and secondary equations to the original equation.
3	Treatment effect on CHD informed by CTTC meta-analysis estimating relative CHD reductions according to absolute LDL reductions, including claiming effects beyond the range observed for the CTTC meta-analysis, and including claiming these effects continue below normal LDL levels, for which benefits have not been observed.	Observed reductions in LDL could be applied to the Framingham risk equations directly.
4	Familial hypercholesterolaemia risk multiplier estimated in comparison with the general population, but then applied to patients with hypercholesterolaemia and a family history of premature CHD.	An appropriate familial hypercholesterolaemia risk multiplier should be applied correctly to the proportion of the overall eligible population who have familial hypercholesterolaemia.
5	Long term treatment effect and adherence: The model based its estimate of ongoing LDL treatment effect on that observed over the duration of the 12-week trials; and based its estimate of the proportion of patients continuing long term treatment on the adherence rate at the end of the 12-week trial.	The mean adherence rates over the duration of the trial should be applied consistently to estimate treatment costs and treatment outcomes.
6	Improve representation of patient variability.	- Run the set of mutually exclusive and exhaustive cohorts (subgroups) through the model - Combine the weighted outputs of each cohort to generate aggregate outputs.
7	Improve tracking of patient characteristics and disease.	Calibrate the multiple cohort approach (as described in 6) to population-level changes in key disease markers.

Drug cost/patient/year

6.26 The annual costs using the published DPMQ for evolocumab are $[redacted] for the 140 mg once fortnightly dose (13 scripts/year), $[redacted] for the 420 mg once monthly dose (12 scripts/year) and for $[redacted] for the 420 mg once fortnightly dose (13 scripts/year assuming maximum quantity increase).

6.27 Using the estimated patient co-payment of $14.98 per script as per the submission and applying the [redacted]% confidential rebate to estimated cost to government, the estimated annual costs using the effective DPMQ are $[redacted] for the 140 mg once fortnightly dose (13 scripts/year), $[redacted] for the 420 mg once monthly dose (12 scripts/year) and for $[redacted] the 420 mg once fortnightly dose (13 scripts/year assuming maximum quantity increase).

6.28 The annual evolocumab costs, regardless of dose, are substantially higher than the annual cost for ezetimibe of $[redacted] (12 scripts/year inclusive of the patient co-payment). The ESC noted that, based on these estimates, evolocumab is greater than [redacted] to [redacted] times the cost of ezetimibe.

Estimated PBS usage & financial implications

6.29 The submission was considered by DUSC. The main issues considered by DUSC were the following.

- The market share approach, based on ezetimibe utilisation, underestimated the population eligible for evolocumab.
- Changing clinical practice, including increased assessment of cardiovascular risk or more widespread treatment to target cholesterol levels, could result in many more patients being treated with evolocumab. Given the high prevalence of dyslipidaemia and the proposed price of evolocumab, small changes in practice could have a large budget impact.
- There is significant potential for use beyond the restriction by patients who are not achieving target cholesterol levels, but who would not qualify for evolocumab treatment under the proposed restriction.

Estimated use and financial implications of listing evolocumab

	Year 1	Year 2	Year 3	Year 4	Year 5
Non-familial hypercholesterolaemia					
Scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to the PBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Heterozygous familial hypercholesterolaemia					
Scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to the PBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Homozygous familial hypercholesterolaemia					
Scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to the PBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total population					
Scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost (DPMQ)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total copayment	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Sponsor rebate	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Changes in use of other therapies	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to the PBS	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**

Abbreviations: FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia.

Source: Compiled during the evaluation using 'Section E.xls' spreadsheet provided with the submission

Note: Corrections for: January 2015 patient co-payments; error in calculating statin copayment for general patients; error in proportion of substituted scripts

6.30 The redacted table above shows that the estimates of utilisation and financial impact in the non-familial and familial hypercholesterolaemia were derived.

6.31 At year 5 of listing, the estimated number of total scripts would be over 200,000 and the net cost to the PBS would be over $100 million.

Financial Management – Risk Sharing Arrangements

6.32 The sponsor recognised the need for an arrangement to address the financial uncertainty associated with the PBS listing of evolocumab and welcomes PBAC feedback on the arrangement required.

6.33 The sponsor requested a special pricing arrangement, where the sponsor would provide a confidential [redacted]% rebate based on total Commonwealth expenditure.

7 PBAC Outcome

7.1 The PBAC rejected the request to list evolocumab for the treatment of hypercholesterolaemia on the basis of unestablished clinical place in therapy and the uncertainty surrounding its use in clinical practice.

7.2 The PBAC noted that the submission was made under the TGA-PBAC parallel process with the TGA Delegate's consideration expected in late 2015. Accordingly, the PBAC noted that there were no TGA documents available during the time of PBAC consideration to determine the indication of the drug and its clinical place in therapy.

7.3 The PBAC noted that, until the TGA Delegate's initial consideration is complete, the DUSC and ESC Advices provided sufficient comment on the clinical claim, economic analysis and financial implications. The PBAC also noted that the DUSC and ESC Advices may need amendment following this TGA consideration of evolocumab.

7.4 The PBAC noted that the sponsor anticipated a deferral or a rejection as the Pre-PBAC response stated that any advice from PBAC and its subcommittees would be assimilated into a planned resubmission. The PBAC noted that the intent of the submission was to initiate a dialogue rather than to request PBS listing. The PBAC did not consider the timing of the submission to be appropriate and stated that it was not an optimal use of time and scarce resources. The PBAC therefore advised the Department to consider amending the guidelines for the TGA-PBAC parallel process to prevent the consideration of such premature submissions in the future.

The PBAC stated that the Public Summary Document (PSD) for evolocumab should be published in accordance with normal timeframes of a 'rejection' agenda item, despite the fact that it would not have received TGA approval by the time of PSD publication. The PBAC considered that this would be appropriate for purposes of transparency and clarity in the process and also for the public interest.

7.5 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Reject

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 intent of submitting this dossier through the TGA-PBAC parallel process was to open a dialogue in good faith with the PBAC to work collaboratively and ensure the best interests of patients were served. Amgen intends to continue to work constructively and collaboratively with the PBAC to secure PBS listing of evolocumab for Australian patients.