7.04 EVOLOCUMAB, 140mg pre-filled injection pen, Repatha®, Amgen.

1 Purpose of Application

1.1 The submission requested a Section 85 Authority Required PBS listing for evolocumab for the treatment of familial hypercholesterolaemia.

2 Requested listing

2.1 The requested PBS listing is presented below.

Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Published (Effective) DPMQ	Proprietary Name and Manufacturer	
EVOLOCUMAB 140mg/mL injection, 1 x 1mL pre-filled injection pen	2	5	$[redacted] ($[redacted])	Repatha®	Amgen

Authority Required

Heterozygous familial hypercholesterolaemia and homozygous familial hypercholesterolaemia

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
Treatment phase	Initial treatment

Clinical criteria:	The treatment must be in conjunction with dietary therapy and exercise. AND Patient must have familial hypercholesterolaemia as determined by a Dutch Lipid Clinic Network Score of greater than or equal to 6 or genetic testing. AND Patient must have coronary heart disease which has become symptomatic; OR Patient must have cerebrovascular disease which has become symptomatic; OR Patient must have genetically confirmed homozygous familial hypercholesterolaemia. AND Patient must have an LDL cholesterol in excess of 3.3 mmol/L after at least 3 months of treatment at a maximum tolerated dose of a statin, in conjunction with dietary therapy and exercise; OR must have developed a clinically important product-related adverse event during treatment with a statin necessitating a reduction in the statin dose; OR must have a contraindication to treatment with a statin.
Prescriber Instructions/ Treatment criteria:	Must be treated by or in consultation with a consultant physician. The date of the consultation must be no more than 3 months prior to the application for a PBS authority. The full name of the medical practitioner consulted and the date of consultation are to be provided at the time of application. 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 dose and duration of statin treatment must be provided at the time of application. 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. The qualifying Dutch Lipid Clinic Network Score or results of genetic testing must be provided at the time of application.

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
Treatment phase	Continuing treatment
Clinical criteria	Patient must have received an initial authority prescription for this drug for the treatment of familial hypercholesterolaemia.

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

2.3 The re-submission stated that the proposed restriction narrowed the eligible population to a small subset of patients with a higher overall cardiovascular risk and therefore greater clinical need compared to the previous March 2015 restriction (which covered a broader hypercholesterolaemia population).

2.4 The ESC agreed that the proposed restriction adequately identified the 'high risk' population, but questioned whether restricting the population to high risk was clinically appropriate.

2.5 The ESC noted that the requirement for patients to be contraindicated to statins was difficult to administer in clinical practice.

2.6 The ESC agreed that it was appropriate to specify a time frame within which the consultation should have occurred, but considered that a time frame of 6 months was more practical.

2.7 The clinical criteria outlined in the proposed listing were more restrictive than the TGA-approved indication, PBS listing of the main comparator, current Australian guidelines and the available clinical evidence. The re-submission claimed that a narrow PBS listing can be implemented through the use of Authority Required listings and limitations on treatment initiation to lipid specialists.

2.8 The PBAC considered that restricting listing to the homozygous FH population would be appropriate given the high clinical need in that population. In this case, homozygous disease should be defined by either a Dutch Lipid Clinic Network Score of 7 or higher, or genetic testing.

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

3 Background

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):
  - 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 TGA indication notes that the effect of evolocumab on cardiovascular morbidity and mortality has not yet been determined.

3.2 The sponsor previously made a submission to the March 2015 PBAC meeting "to open a dialogue regarding the potential future listing of evolocumab on the PBS for the treatment of hypercholesterolaemia". The PBAC considered that the submission did not represent an appropriate use of the TGA-PBAC parallel process pathway. The PBAC noted that the DUSC and ESC Advices provided sufficient comment on the clinical claim, economic analysis and financial implications.

3.3 The PBAC rejected the submission on the basis of unestablished clinical place in therapy and the uncertainty surrounding its use in clinical practice.

Key differences between the previous submission and current re-submission

	March 2015 submission	Current re-submission
Requested PBS listing	Treatment of patients with hypercholesterolaemia (familial and non-familial) who still had high LDL levels despite optimal therapy	- Secondary prevention of cardiovascular events in patients with heterozygous familial hypercholesterolaemia who still had high LDL levels despite optimal treatment - Treatment of homozygous familial hypercholesterolaemia
Basis of comparison	- Series of direct comparisons of evolocumab vs. ezetimibe and placebo (RUTHERFORD-2, TESLA, GAUSS-2, LAPLACE-2, MENDEL-2 - Supportive comparison of longer term outcomes with evolocumab vs. standard of care from pragmatic RCTs/observational studies (DESCARTES, OSLER-1, OSLER-2, TAUSSIG)	Same core evidence base as previous submission with two additional analyses - Updated exploratory analyses of cardiovascular outcomes reported in the OSLER long-term studies - Supportive indirect comparison of evolocumab vs alirocumab using either placebo or ezetimibe as a common comparator.
Modelled patient population	Derived from the individual trial populations with additional synthesised patient characteristics	Characteristics of the modelled population synthesized from Australian AUSDIAB FH population and post-hoc subgroup analyses of secondary prevention patients with LDL > 3.3 in evolocumab clinical trial program
Underlying cardiovascular risk calculation	Calculated based on the Framingham primary prevention risk equation with and without a familial hypercholesterolaemia risk multiplier	Calculated based on the Framingham secondary prevention risk equation (MI, CHD death) and Framingham stroke equation (IS) with a familial hypercholesterolaemia risk multiplier
Impact of previous events on future	- Prior event multiplier estimated by comparing difference in events between	- Prior event multiplier based on observational data from UK CPRD GOLD database.

events	Framingham primary prevention and secondary prevention risk equations. - Distribution of future events were not affected by the type of previous event - Mortality multiplier estimated from observational studies	- Distribution of events (including fatal events) also based on observational data from the UK CPRD GOLD database.
Treatment adherence	Estimated 95% treatment adherence. Implemented as a 5% reduction in drug costs	Assumed 100% treatment adherence
Drug costs	Based on effective prices for January 2015 PBS schedule	Based on effective prices for October 2015 PBS schedule
Economic model structure	Four health states - Primary prevention setting - Secondary prevention following a MI - Secondary prevention following a IS - Death Various analyses of the previous model included patients with and without a prior cardiovascular event	Five core health state - MI (no history of IS) - MI (history of IS) - IS (with or without history of MI) - Cardiovascular death - Non-cardiovascular death The three non-fatal health states have acute sub-states to account for the first year following an event. The model updates annually (based on patient age). All patients start the model with a prior cardiovascular event
Modelled economic results	Treatment with evolocumab was associated with costs per QALY gained of $45, 000/QALY - $75,000/QALY against ezetimibe and $45, 000/QALY - $75,000/QALY against placebo in patients with heterozygous familial hypercholesterolaemia	Treatment with evolocumab was associated with costs per QALY gained of $15,000/QALY - $45,000/QALY against ezetimibe and $15,000/QALY - $45,000/QALY against placebo in patients with heterozygous familial hypercholesterolaemia
Expected utilisation of evolocumab	Mixed market share (based on ezetimibe)/ epidemiology approach to estimate utilisation in non-familial and familial hypercholesterolaemia	Epidemiology approach to estimate utilisation in familial hypercholesterolaemia
Cumulative scripts/ cost to the PBS over 5 years	Cumulative net cost over five years of more than $100 million.	Cumulative net cost over five years of more than $100 million.

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

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 re-submission claimed that evolocumab would replace or be used in addition to other non-statin therapies for familial hypercholesterolaemia.

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

5 Comparator

5.1 The re-submission nominated both ezetimibe and placebo as the main comparators. This was appropriate.

5.2 The re-submission also nominated alirocumab as a secondary comparator. This was appropriate. This comparison was considered as supportive evidence during the evaluation as alirocumab is not TGA approved or PBS listed for use in Australia. The ESC agreed with the PSCR (p2) that this indirect comparison is not currently relevant for PBAC decision making.

5.3 Other non-statin therapies could also be relevant secondary comparators (fibrates, bile acid sequestrants, nicotinic acid derivatives).

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician presented clinical case studies and discussed the natural history of the disease, how the drug would be used in practice, and addressed other matters in response to the Committee's questions.

6.2 The PBAC did not consider that the hearing added substantively to the evidence presented in the submission, but noted that the clinician suggested there might be a reduction in lipid apheresis for some patients.

Consumer comments

6.3 The PBAC noted and welcomed the input from individuals (10), health care professionals (2) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with evolocumab including fewer side effects, reduction in LDL apheresis, and an increased overall quality of life.

6.4 The PBAC noted the input received from the Chair of the Familial Hypercholesterolaemia Australasia Network clarifying the clinical need and potential benefits of evolocumab. The PBAC specifically noted that evolocumab will provide an additional treatment option for patients who have not been able to lower their LDL levels sufficiently using standard treatments. The advice also noted the potential for savings in health expenditure due to reduced LDL apheresis, heart attacks, and related complications.

6.5 The PBAC noted the input received from FH Family Support Group of Western Australia (FHSG) clarifying the clinical place and potential benefits of evolocumab. The PBAC specifically noted that the reduction of LDL cholesterol, and associated reduction in coronary artery disease, would allow patients to remain productive and

healthy members of society and cost less to society due to reduced cardiovascular events and need for medical procedures.

Clinical trials

6.6 The re-submission was based on a series of comparisons between evolocumab and nominated comparators. The direct comparisons presented in the resubmission are the same studies presented previously. New/updated data were presented as supportive.

- Direct comparison of evolocumab vs. placebo as an adjunct to standard care in patients with heterozygous familial hypercholesterolaemia who have failed to achieve adequate control with lipid-lowering medications (RUTHERFORD-2).
- Direct comparison of evolocumab vs. placebo as an adjunct to standard care in patients with homozygous familial hypercholesterolaemia who have failed to achieve adequate control with lipid-lowering medications (TESLA).
- Direct comparison of evolocumab vs. ezetimibe in patients with hypercholesterolaemia (familial and non-familial) who are statin intolerant (GAUSS-2), or who have failed to achieve adequate control with statin therapy (LAPLACE-2), or as first-line therapy in patients with low-cardiovascular risk (MENDEL-2).
- Supportive comparison of longer term outcomes with evolocumab vs. standard of care in patients with hypercholesterolaemia (familial and non-familial) from pragmatic RCTs/observational studies (DESCARTES, OSLER-1, OSLER-2, TAUSSIG). This was updated from the previous March 2015 submission.
- Supportive indirect comparison of evolocumab vs alirocumab in patients with hypercholesterolaemia (familial and non-familial) using either placebo or ezetimibe as a common comparator. This was a new comparison not previously considered in the March 2015 submission.

6.7 Details of the key trials and supportive longer-term studies are provided in the table below.

Table 1: Trials and associated reports included in the re-submission

Trial ID	Protocol title/ Publication title	Publication citation
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 hypercholesterolaemia. Part A – Open-label, Single-arm, Multicenter Pilot Study to Evaluate Safety, Tolerability and Efficacy of AMG 145 in Subjects With Homozygous Familial hypercholesterolaemia. Part B – Double-blind, Randomised, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of AMG 145 in Subjects With Homozygous Familial hypercholesterolaemia	Internal study report
	Raal F et al (2015). Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial.	Lancet 9965: 341-350
	Stein EA et al (2013). Effect of the proprotein convertase subtilisin/kexin 9 monoclonal antibody, AMG 145, in homozygous familial hypercholesterolaemia	Circulation 128: 2113–2120
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	Internal study report

Trial ID	Protocol title/ Publication title	Publication citation
	Framingham Risk Score of 10% or Less	
	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
	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 hypercholesterolaemia 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 hypercholesterolaemia 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 hypercholesterolaemia.	Internal study report
	Ral 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
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 hypercholesterolaemia: 52-week results from the open-label study of long-term evaluation against LDL-C (OSLER) randomized trial	Circulation 129: 234–243
	Sabatine MS et al (2015). Efficacy and safety of evolocumab in	New England Journal

Trial ID	Protocol title/ Publication title	Publication citation
	reducing lipids and cardiovascular events	of Medicine 372:1500-1509
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]
	Sabatine MS et al (2015). Efficacy and safety of evolocumab in reducing lipids and cardiovascular events	New England Journal of Medicine 372:1500-1509
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 hypercholesterolaemia	Internal study report [Interim July 2014]

Source: Table B.2-3 (p 26-31) of the re-submission; evolocumab search results, Attachment 2 of the re-submission; alirocumab search results, Appendix 2 of the re-submission
Note: Abstracts of studies with full publications are not presented

6.8 A clinical outcomes study comparing evolocumab vs placebo as an adjunct to standard care in patients with hypercholesterolaemia and cardiovascular disease is due to report in 2018 (FOURIER).

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

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome	Use in modelled evaluation
Evolocumab vs placebo						
RUTHERFORD-2	331	MC, R, DB, PG, PC 4 treatment arms 12 weeks	Low	HeFH	Change in LDL levels	LDL levels
TESLA	50	MC, R, DB, PG, PC 4 treatment arms 12 weeks	Low	HoFH	Change in LDL levels	Not used
Evolocumab vs ezetimibe						
GAUSS-2	307	MC, R, DB, PG, AC 4 treatment arms 12 weeks	Low	Statin-intolerant patients	Change in LDL levels	Not used
LAPLACE-2	2,067	MC R, DB, PG, AC, PC 24 treatment arms 12 weeks	Low	Patients requiring combination with statin	Change in LDL levels	LDL levels
MENDEL-2	615	MC, R, DB, PG, AC, PC 6 treatments arms 12 weeks	Low	Low-risk patients requiring monotherapy	Change in LDL levels	Not used
Evolocumab supportive studies						
DESCARTES vs placebo	905	MC, R, DB, PG, PC 4 treatment arms 52 weeks	Low	Patients failing current therapies	Change in LDL levels	Not used
OSLER-1 vs standard care	1,324	MC, R, OL, PG 52 weeks with extension up to 5 years	High	Patients from evolocumab Phase II trials	Adverse events	Not used
OSLER-2 vs standard care	3,121	MC, R, OL, PG 52 weeks with extension up to 5 years	High	Patients from evolocumab Phase III trials	Adverse events	Not used
TAUSSIG	238	Extension study up to 5 years	High	Severe FH	Adverse events	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

Comparative effectiveness

6.10 LDL outcomes with evolocumab compared to ezetimibe or placebo were unchanged from the previous March 2015 submission.

6.11 Table 3 summarises the mean change in LDL levels from baseline with evolocumab and placebo in patients with heterozygous familial hypercholesterolaemia.

Table 3: Mean percent change in calculated LDL levels in patients with heterozygous familial hypercholesterolaemia

Trial	Evolocumab, Mean (95% CI)	Placebo, Mean (95% CI)	Treatment difference, Mean (95% CI)
Baseline to Week 10/12			
Fortnightly dosing N = 164	-62.7% (-66.2, -59.2)	-1.4% (-6.3, 3.6)	-61.3% (-67.2, -55.4)
Monthly dosing N = 165	-64.7% (-68.1, -61.4)	1.5% (-3.2, 6.2)	-66.2% (-71.9, -60.6)

Abbreviations: CI, confidence interval; LDL, low-density lipoprotein; SD, standard deviation
Source: Table B.6-1 (p 64) of the re-submission

6.12 Treatment with evolocumab (fortnightly and monthly dosing) was associated with statistically significant decreases in LDL levels compared to placebo (approximately 60-65% reduction) in patients with heterozygous familial hypercholesterolaemia not achieving cholesterol targets with statin and non-statin therapies.

6.13 Table 4 summarises the mean change in LDL levels from baseline with evolocumab and placebo in patients with homozygous familial hypercholesterolaemia.

Table 4: 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)
Baseline to Week 12			
Monthly dosing N = 49	-23.1% (-30.8, -15.4)	9.0% (-1.5, 19.6)	-32.1% (-45.1, -19.2)

Abbreviations: CI, confidence interval; LDL, low-density lipoprotein; SD, standard deviation
Source: Table B.6-1 (p 64) of the re-submission

6.14 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 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.

6.15 Treatment with evolocumab (fortnightly and monthly dosing) was associated with statistically significant decreases in LDL levels compared to ezetimibe (approximately 40% reduction) in mixed hypercholesterolaemia populations (including familial and non-familial patients).

6.16 Longer term studies suggest that short-term improvements in LDL levels may be maintained beyond 2 years while patients continue to be treated with evolocumab.

6.17 The re-submission presented an updated analysis of cardiovascular events reported in the OSLER trials.

Table 5: Adjudicated cardiovascular events[a]

Trial	Evolocumab, n/N	Standard-of-care[b], n/N	Hazard ratio (95% CI)
OSLER-1 [Year 1] (Koren et al 2014)	9/736 (1.2%)	8/368 (2.2%)	NR
Interim combined OSLER analysis [Year 1] (July 2014 cutoff, March 2015 submission)	(0.9%)	(1.7%)	NR
Interim combined OSLER analysis [Year 1] (January 2015 cutoff, Sabatine et al 2015)	29/2976 (1.0%)	31/1489 (2.2%)	0.47 (0.28, 0.78)

Abbreviations: CI, confidence interval; NR, not reported

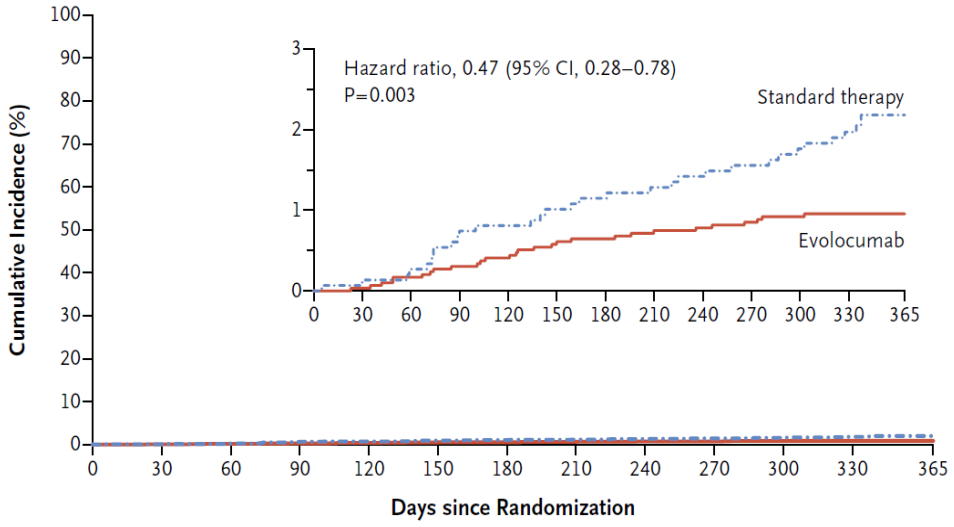
Source: Figure B-6.9 (p 76) of the re-submission; Table C-3.3 (p 114-128) of the March 2015 submission

[a] Includes death by any cause, cardiovascular death, myocardial infarction, hospitalisation for unstable angina, coronary revascularisation, stroke, transient ischaemic attack, hospitalisation for heart failure.

[b] Standard of care typically represents the treatment patients were previously receiving in the control arms of the parent trials

6.18 Based on an exploratory analysis of longer term studies, treatment with evolocumab was associated with a statistically significant reduction in cardiovascular events (primarily coronary revascularisation procedures) compared to standard care after one year of treatment (HR 0.47; 95% CI 0.28, 0.78).

Figure 1: Cumulative incidence of CV events in OSLER 1/2



Source: Figure B.6-9, p76 of the re-submission

Notes: Included among the cardiovascular events were death, myocardial infarction, unstable angina requiring hospitalization, coronary revascularization, stroke, transient ischemic attack, and hospitalization for heart failure. Cardiovascular events were reported in 29 of 2976 patients in the evolocumab group (Kaplan–Meier 1-year event rate, 0.95%) and in 31 of 1489 patients in the standard-therapy group (Kaplan–Meier 1-year event rate, 2.18%). The inset shows the same data on an expanded y axis. The P value was calculated with the use of a log-rank test.

6.19 There were a number of limitations with the cardiovascular event analysis including: potential bias introduced by the open-label study design (different management decisions in different treatment arms), potential selection bias (as the OSLER studies only included patients who had successfully completed the parent studies), limited

applicability (as patients may not have been using optimal therapy based on underlying risk) as well as low event frequency.

6.20 Results were broadly consistent with analyses reported from a long-term study of alirocumab (ODYSSEY LONG TERM) as well as a broader systematic review of PCSK9 therapies (Navarese et al 2015).

Comparative harms

6.21 Safety data remained unchanged from the previous March 2015 submission.

6.22 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.

6.23 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).

6.24 There are limited long-term safety data available for evolocumab.

6.25 The re-submission did not present any assessment of comparative safety between evolocumab and alirocumab.

Benefits/harms

6.26 On the basis of direct evidence presented in the re-submission, the comparison of evolocumab (fortnightly/monthly) and placebo in patients with heterozygous familial hypercholesterolaemia resulted in:

- Approximately a 60% relative reduction in LDL levels over a 12-week treatment duration.
- No apparent difference in adverse events over a 12-week treatment duration.

6.27 On the basis of direct evidence presented in the re-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.

6.29 On the basis of direct evidence presented in the re-submission, the comparison of evolocumab (fortnightly/monthly) and ezetimibe in patients with hypercholesterolaemia (mixed familial and non-familial) 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.

6.30 Current data are inadequate to reliably inform the comparison of evolocumab and alirocumab.

Clinical claim

6.31 The submission described evolocumab as superior in terms of efficacy (based on surrogate outcome measures) and similar in terms of safety compared to ezetimibe. This claim may be reasonable.

6.32 The submission described evolocumab as superior in terms of efficacy (based on surrogate outcome measures) and similar in terms of safety compared to placebo. This claim may be reasonable.

6.33 The submission described evolocumab as superior in terms of efficacy (based on surrogate outcome measures) compared to alirocumab but made no claim regarding comparative safety. The claim of superiority was not well supported.

6.34 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 might translate into meaningful reductions in cardiovascular events. However, the magnitude of benefit remains unclear.

6.35 The PBAC considered that the claim of superior comparative effectiveness, in terms of reduction in LDL levels, was reasonable adequately supported by the data.

6.36 The PBAC considered that the claim of non-inferior comparative safety was adequately supported by the data.

Economic analysis

6.37 The re-submission presented a modelled economic analysis assessing the cost-effectiveness of fortnightly evolocumab when used as a replacement or as an add-on therapy to ezetimibe in patients with heterozygous familial hypercholesterolaemia.

6.38 No economic evaluation was presented for the use of evolocumab in patients with homozygous familial hypercholesterolaemia.

6.39 No economic evaluation was presented for the use of monthly evolocumab in patients with heterozygous familial hypercholesterolaemia.

Table 6: Summary of model structure and rationale

Methods used to generate results	Markov cohort expected value analysis
Time horizon	35 years
Cycle length	Monthly
Treatments	Evolocumab, ezetimibe, placebo
Health states	Myocardial infarction (with no history of stroke), myocardial infarction (with a history of stroke), stroke (with or without a history of myocardial infarction), cardiovascular death and non-cardiovascular death. The model also included acute sub-states to account for the first 11 months after a non-fatal event.
Transition probabilities	Transition probabilities were derived from the composite annual event rates (Framingham risk equations with familial hypercholesterolaemia multiplier and prior recent event multiplier within 12 months of an event) adjusted for the composite relative event rate associated with the reduction in LDL from treatment, adjusted for the one month cycle length and transformed into probabilities. Probabilities are 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.
Outcomes	% reduction in LDL; life years; quality-adjusted life years
Discount rate	5% for costs and outcomes
Software package	Excel 2010

Source: Constructed during the evaluation

6.40 Compared to the March 2015 submission the current model has changed patient population characteristics, calculation of underlying cardiovascular risk, prior event risk multiplier, treatment adherence rates, drug costs and model structure (additional health states and annual updating).

6.41 The economic analysis should be interpreted with caution as the approach used in the submission lacked transparency and was reliant on complex methods to populate the model.

6.42 The National Lipid Association Expert Panel on Familial Hypercholesterolemia have noted that standard Framingham or other risk classification schemes are not applicable to individuals with FH [Youngblom & Knowles, 2014].

6.43 Benn et al (2012) compared risk of coronary arterial disease (CAD) for individuals with a diagnosis of definite/probable and possible FH relative to those with unlikely FH adjusting for gender, age, BMI, hypertension, metabolic syndrome, diabetes mellitus, and smoking. Without adjusting for LDL the estimated multiplier is double counting the effect of raised LDL in FH patients. LDL is a key input to the Framingham equations that determine baseline risk, and LDL is likely a key factor driving the observed differences in CAD in the Benn study.

6.44 The results of the Benn study did not provide any support the application of a FH risk multiplier in the model (it should be set to 1). Supplementary analyses might compare Framingham derived risk estimates for a typical population without raised cholesterol (representing the general population off treatment group in the Benn study); a typical non-FH population on treatment for raised cholesterol; and an FH population. The resulting relative risk ratios could be compared to the odds ratios reported by Benn et al to provide some form of validation for the model's input parameters. The odds ratio of the definite/probable FH group to the on treatment general population group is approximately 2 (though the lower 95% CI is likely to be around 1.4).

6.45 The application of multipliers of 2 to 3 to first year event probabilities to represent increased risk in the first year after the experience of an event is inappropriate. The baseline event rates (to which the first year multipliers were applied) seem to have been converted from 4 and 10 year event rates for MI and IS, respectively. These event rates include events in the first year. To require the application of the multipliers the estimated transition probabilities would have been estimated using data describing events from the end of the first year after an event. Otherwise event rates in the first year are being multiplied inappropriately.

6.46 The estimation of constant baseline event probabilities using 4 and 10 year event rates overestimates the long-term event probabilities because the observed data include year 1 event rates, inappropriately increasing the post-year 1 event probabilities. The model should estimate separate event probabilities for year 1 and post-year 1 time periods.

6.47 Key issues with the economic model are summarised in the following table.

Table 7: Key issues with the model

Description	Method/Value	Impact
Modelled patient population	Characteristics of the modelled population synthesised from Australian AUSDIAB FH population and post-hoc subgroup analyses of secondary prevention patients with LDL > 3.3 in evolocumab clinical trial program	High, favours evolocumab
Underlying cardiovascular risk	Estimated by applying Framingham risk equations to synthesised population and applying a familial hypercholesterolaemia multiplier (based on observation data from the Simon-Broome Register) and a prior event multiplier for the first year following an event in the model (based on observational data from UK CPRD GOLD database).	High, favours evolocumab
Transformation of LDL outcomes to cardiovascular outcomes	Relative LDL measures converted to absolute measures based on the synthesised population. Absolute estimates converted to relative rate ratios in cardiovascular events using the CTTC analysis.	Moderate, favours evolocumab
Treatment adherence	Assumed perfect adherence	Unclear

Source: compiled during the evaluation

6.48 The results of the economic model are summarised below.

Table 8: Modelled economic analyses

	Evolocumab	Placebo	Increment
Costs	$ [redacted]	$ [redacted]	$ [redacted]
Lys	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost per LY gained			**$** [redacted]
Incremental cost per QALY gained			**$** [redacted]
	Evolocumab	**Ezetimibe**	**Increment**
Costs	$ [redacted]	$ [redacted]	$ [redacted]
Lys	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost per LY gained			**$** [redacted]
Incremental cost per QALY gained			**$** [redacted]

Abbreviations: LY, life year; QALY, quality-adjusted life year

Source: Table D.5-2 (p 165), Table D.5-3 (p 165) of the re-submission

Note: Estimates are based on corrected drug costs (fixed incorrect monthly adjustment, inappropriate exclusion of patient co-payments from evolocumab price and 5% mandatory reduction for ezetimibe)

The redacted table shows ICERS in the range of $15,000/QALY - $45,000/QALY.

6.49 Based on the economic model, treatment with evolocumab was associated with a cost per QALY gained of $15,000/QALY - $45, 000/QALY compared to placebo and 15,000/QALY - $45, 000/QALY compared to ezetimibe (ICERs were re-estimated during the evaluation, as there were errors in the submission's calculations of drug cost). These estimates should be interpreted with caution given concerns regarding the calculation of baseline risk and the inherent uncertainty associated with the transformation of LDL levels to cardiovascular outcomes.

6.50 The March 2015 submission estimated that treatment with evolocumab was associated with costs per QALY gained of $45,000/QALY - $75,000/QALY against placebo and $45,000/QALY - $75,000/QALY against ezetimibe in patients with heterozygous familial hypercholesterolaemia. The difference in cost-effectiveness is primarily due to the increased underlying cardiovascular risk in the current model.

6.51 The results of the sensitivity analyses indicate that the model is most sensitive to underlying cardiovascular risk (particularly the use of a familial hypercholesterolaemia risk multiplier), age (primarily through impact on underlying cardiovascular risk) and time horizon.

Table 9: Results of univariate sensitivity analyses

Univariate analysis	ICER (per QALY) vs ezetimibe	ICER (per QALY) vs placebo
Base case	$	$
Time horizon (base case: 35 years)		
15 years	$	$
Age at model entry (base case: 62 years)		
45 years	$	$
75 years	$	$
Familial hypercholesterolaemia event rate multiplier (base case: 4)		
1	$	$
2	$	$
8	$	$

Abbreviations: CHD: coronary heart disease; ICER: incremental cost-effectiveness ratio; MI: myocardial infarction; QALY: quality adjusted life year

Source: Constructed during the evaluation using the model 'Evolocumab model_Nov15' provided with the re-submission

Note: Estimates are based on corrected drug costs

6.52 The model was sensitive to interactions between the three major components of underlying risk in the model (Framingham risk calculator estimates, familial hypercholesterolaemia risk multiplier and prior event risk multiplier). Many plausible combinations of the risk components resulted in very-high incremental cost-effectiveness ratios.

6.53 The results of alternative economic analyses in which both multipliers are removed are presented below. There remains uncertainty regarding the magnitude of the non-multiplied treatment effect.

Table 10: Alternative economic analyses (no familial hypercholesterolemia or prior event multiplier)

	Evolocumab	Placebo	Increment
Costs	$	$	$
LYs			
QALYs			
Incremental cost per LY gained			**$**
Incremental cost per QALY gained			**$**
	Evolocumab	**Ezetimibe**	**Increment**
Costs	$	$	$
LYs			
QALYs			
Incremental cost per LY gained			**$**
Incremental cost per QALY gained			**$**

Abbreviations: LY, life year; QALY, quality-adjusted life year

Source: Constructed using the spreadsheet model 'Evolocumab model_Nov15' provided with the submission

The redacted table shows ICERS in the range of $105,000/QALY - $200,000/QALY.

Drug cost/patient/year:

6.54 The annual costs using the published DPMQ for evolocumab are $ for the 140mg once fortnightly dose (2 injections per script, 13 scripts/year), $ for the 420mg once monthly dose (3 injections per script, 12 scripts/year) and $ for the 420mg once fortnightly dose (6 injections per script, 13 scripts/year).

6.55 Using the estimated patient co-payment of $ per script as per the submission

and applying the [redacted]% confidential rebate to estimate cost to government, the estimated annual costs using the effective DPMQ are $[redacted] for the 140mg once fortnightly dose, $[redacted] for the 420mg once monthly dose and $[redacted] for the 420mg once fortnightly dose.

6.56 The annual evolocumab costs, regardless of dose, are substantially higher than the annual cost for ezetimibe of $[redacted] (12 scripts/year includes 5% mandatory price reduction in April 2016).

Estimated PBS usage & financial implications

6.57 This re-submission was not considered by DUSC.

6.58 The re-submission used an epidemiological approach to estimate the utilisation/ financial implications associated with the PBS listing of evolocumab for heterozygous familial hypercholesterolaemia and homozygous familial hypercholesterolaemia.

Table 11: Estimated utilisation and cost to the PBS in the first five years of listing

	Year 1 (Aug 2016-Jul 2017)	Year 2 (Aug 2017-Jul 2018)	Year 3 (Aug 2018-Jul 2019)	Year 4 (Aug 2019-Jul 2020)	Year 5 (Aug 2020-Jul 2021)
Australian FH population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heterozygous familial hypercholesterolaemia					
Australian HeFH patients the meet PBS criteria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab uptake rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total evolocumab scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost (published DPMQ)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Patient co-payments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Sponsor rebate ([redacted]%)	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Substitution of ezetimibe	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Costs for concurrent statins to replace FDCs	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to the PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Homozygous familial hypercholesterolaemia					
Australian HoFH patients the meet PBS criteria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab uptake rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scripts (fortnightly dosing)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scripts (monthly dosing)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost (published DPMQ)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Patient co-payments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Sponsor rebate ([redacted]%)	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to the PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total population					
Net cost to the PBS/RPBS	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**

Abbreviations: FDC, fixed dose combination; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia.

Source: Table E.2-1 (p 180), Table E.2-2 (p 181), Table E.3-1 (p 182), Table E.3-2 (p 182), Table E.4-1 (p 183) of the re-submission

The redacted table shows that at year 5, the estimated number of patients overall was 10,000 – 50,000 per year and the net cost to the PBS would be $30 - $60 million per year.

6.59 The estimated cost of listing evolocumab on the PBS is highly uncertain due to assumptions regarding the proportion of patients diagnosed with familial hypercholesterolaemia (likely to increase with the listing of evolocumab), the proportion of patients eligible for treatment under the proposed restriction and likely treatment adherence in clinical practice.

6.60 Although similar in terms of overall budget impact, there were major differences in the utilisation estimates with the current model suggesting a much larger overall market size for familial hypercholesterolaemia (based on an epidemiological vs. market share approach) which was offset by a more restrictive listing in the current re-submission compared to the previous March 2015 submission.

6.61 There is potential for use of evolocumab outside the requested indication in patients not achieving treatment goals with existing therapy but who do not satisfy the proposed clinical criteria for evolocumab. This risk may be partially mitigated by the use of Authority Required restrictions, specialist prescribers and Risk Share Arrangements.

Financial Management – Risk Sharing Arrangements

6.62 The sponsor expressed a willingness to enter into a Risk Share Arrangement to address the financial uncertainty associated with the PBS listing of evolocumab.

6.63 The sponsor requested a Special Pricing Arrangement, where the sponsor would provide a confidential [redacted]% rebate based on total Commonwealth expenditure.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of evolocumab, under Section 85 Authority Required, for the homozygous familial hypercholesterolaemia population (but not the broader heterozygous familial hypercholesterolaemia population). In making this recommendation, the PBAC considered that the homozygous FH population represent a small, definable, patient group, in whom there is a high level of clinical need.

HETEROZYGOUS

7.2 The PBAC agreed that the proposed restriction adequately identified patients at high risk of CAD.

7.3 The PBAC accepted both ezetimibe and placebo as appropriate comparators in the heterozygous FH population.

7.4 The PBAC accepted the clinical trial evidence that demonstrated a statistically significant decrease in LDL outcomes when treated with evolocumab compared to ezetimibe or placebo, but considered that the translation of these changes to outcomes was important for the assessment of the heterozygous population. The PBAC noted the Sponsor's advice that the FOURIER study is expected to report mortality outcomes towards the end of 2016.

7.5 The PBAC noted that the data for comparative harms were highly variable between trials and did not consistently favour evolocumab, ezetimibe or placebo. There was also no apparent difference in the incidence of adverse events with either fortnightly or monthly dosing of evolocumab.

7.6 The PBAC noted that the issues raised by the ESC concerning the cost-effectiveness of evolocumab stemmed largely from the uncertainty associated with estimating cardiovascular risk from the available data. These issues may be resolved when mortality data become available. Overall, the PBAC considered that the cost-effectiveness of evolocumab when used to treat heterozygous FH was unacceptably high and uncertain, and that further clinical evidence for this population was required.

7.7 The PBAC noted that the estimated cost of listing evolocumab on the PBS was highly uncertain due to assumptions regarding the proportion of patients diagnosed with FH, the proportion of patients eligible for treatment under the proposed restriction and likely treatment adherence in clinical practice.

HOMOZYGOUS

7.8 The PBAC considered that the restrictions for the homozygous group to be complex and will require consultation with the Restrictions Working Group.

7.9 In regard to the recommended listing for the treatment of patients with homozygous FH, the PBAC considered that the restriction should include the requirement for a diagnosis of homozygous FH, as defined either by a score of seven (7) or more in the Dutch Lipid Clinic criteria or by genetic test, prior to treatment.

7.10 The PBAC considered that the most relevant comparator in the homozygous FH population was placebo, as evolocumab is likely to be used as add-on treatment in this population.

7.11 The PBAC accepted the clinical trial evidence that demonstrated a statistically significant decrease in LDL outcomes for homozygous FH patients treated with evolocumab. The PBAC considered that reduction of LDL was a clinically meaningful outcome for the homozygous FH population.

7.12 The PBAC noted that advice from the clinician at the hearing supported the submission's claim that the use of evolocumab in homozygous familial

hypercholesterolaemia may reduce the need for lipid apheresis in some patients. Costs of lipid apheresis were not included in the cost-effectiveness model.

7.13 The PBAC noted that no economic evaluation was presented specifically for the use of evolocumab in patients with homozygous familial hypercholesterolaemia. The PBAC considered that although the cost-effectiveness of evolocumab was likely to be higher than might otherwise be considered acceptable, this was reasonable given the high clinical need for those affected by homozygous familial hypercholesterolaemia.

7.14 The PBAC considered that the submission's estimates of usage in the homozygous FH population were more reliable than the estimates for the heterozygous FH population, as there are likely to be less undiagnosed homozygous patients. The PBAC recommended an RSA that should include a cap, based on the number of patients treated (consistent with the estimates in the submission for the homozygous FH population) with [redacted]% rebate for use above the Cap in any year.

7.15 Under Section 101(3BA) of the National Health Act 1953, the PBAC advised that evolocumab should not be treated as interchangeable on an individual patient basis with any other drugs.

7.16 The PBAC advised evolocumab is not suitable for prescribing by nurse practitioners.

7.17 The PBAC recommended that the Early Supply Rule should apply.

7.18 The PBAC noted that this submission is not eligible for an Independent Review as it was recommended.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:
Restriction to be finalised

9 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.

10 Sponsor's Comment

Amgen is pleased that the PBAC recognises the very high cardiovascular risk of patients with familial hypercholesterolaemia and that treatment of these patients with evolocumab results in clinically meaningful reductions in LDL-C.

Amgen intends to continue to work constructively with the PBAC towards reimbursement for all patients in whom there is clinical need in this setting. Note on timing of the FOURIER trial (mentioned in 6.8 and 7.4 above): The analysis of FOURIER, the evolocumab trial investigating cardiovascular and mortality outcomes, is event-driven and hence there is a degree of uncertainty in the timing of its reporting. FOURIER is anticipated to report no later than 2018* but the precise timing is unknown.

* www.clinicaltrials.gov accessed on 15 June 2016.