7.04 EVOLOCUMAB, Injection 420 mg in 3.5 mL single use pre-filled cartridge, Injection 140 mg in 1 mL single use pre-filled pen, Repatha®, Amgen

1 Purpose of application

1.1 The resubmission requested an extension of the current Section 85 (Authority Required) listing for evolocumab to include the treatment of heterozygous familial hypercholesterolaemia (patients with atherosclerotic disease or very high LDL-c levels).

1.2 The resubmission also requested a new Section 85 (Authority Required) listing for evolocumab for the treatment of non-familial hypercholesterolaemia patients with established atherosclerotic disease.

1.3 The PBAC has previously considered three submissions for evolocumab, at the March 2015 (for patients with familial hypercholesterolaemia and high risk non-familial hypercholesterolaemia), March 2016 (for patients with familial hypercholesterolaemia) and July 2017 (requested listing of a different evolocumab preparation) meetings.

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

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

Component	Description
Population	Patients with heterozygous familial hypercholesterolaemia (FH) with or without atherosclerotic cardiovascular disease (ASCVD) or non-FH with established ASCVD who have not achieved target LDL-c levels despite treatment with maximal tolerated dose of a statin or who are statin-intolerant
Intervention	Evolocumab 140 mg subcutaneous injection every fortnight or evolocumab 420 mg subcutaneous injection every month
Comparator	Ezetimibe 10 mg oral tablet once daily, placebo, alirocumab 75 to 150 mg subcutaneous injection every fortnight or alirocumab 300 mg subcutaneous injection every month
Outcomes	Reduction in LDL-c leading to a reduction in major cardiovascular events (e.g. cardiovascular death, myocardial infarction, stroke)
Clinical claim	Evolocumab is superior in terms of efficacy and similar in terms of safety compared to ezetimibe, placebo and 75 mg alirocumab. The Pre-Sub-Committee Response (PSCR) (p3) claimed evolocumab is at least as effective as the alirocumab higher dose regimen (titration 75-150 mg fortnightly, 150 mg fortnightly).

Source: Table 1.1.1 (p 13-14) of the resubmission

2 Requested listing

2.1 The resubmission requested an extension of listing to broaden the existing listing for homozygous FH to also include heterozygous FH patients with high cardiovascular risk (patients with ASCVD and/or very high LDL-c levels). Amendments to the current restriction are in bold and deletions are in strikethrough.

2.2 The resubmission also requested a new listing for the treatment of non-FH patients with established ASCVD.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Published (Effective) Dispensed price for maximum quantity	Proprietary Name and Manufacturer	
EVOLOCUMAB					
140 mg/mL injection, 1 mL injection device	2	5	$629.84 ($[redacted])	Repatha Sureclick®	Amgen
120 mg/mL injection, 3.5 mL injection device	1	5	$682.33 ($[redacted])	Repatha Automated Mini-Doser®	

Category / Program:	General Schedule
PBS Indication:	Familial ~~homozygous~~ hypercholesterolaemia
Restriction:	Authority required – in writing
Clinical criteria:	The treatment must be in conjunction with dietary therapy and exercise AND The condition must have been confirmed by genetic testing; OR The condition must have been confirmed by a Dutch Lipid Clinic Network Score of at least ~~7~~ **6** AND Patient must have an LDL-c cholesterol level in excess of **5** ~~3.3 millimoles per litre~~, or **3.3 mmol/L in the presence of symptomatic atherosclerotic cardiovascular disease**, after at least 3 months of treatment at a maximum tolerated dose of an HMG CoA reductase inhibitor (statin), in conjunction with dietary therapy and exercise; OR Patient must have an LDL-c cholesterol level in excess of **5** ~~3.3 millimoles per litre~~, or **3.3 mmol/L in the presence of symptomatic atherosclerotic cardiovascular disease**, after having developed a clinically important product-related adverse event during treatment with an HMG CoA reductase inhibitor (statin) necessitating a withdrawal of statin treatment; OR Patient must have an LDL-c cholesterol level in excess of **5** ~~3.3 millimoles per litre~~, or **3.3 mmol/L in the presence of symptomatic atherosclerotic cardiovascular disease**, and must be one in whom treatment with an HMG CoA reductase inhibitor (statin) is contraindicated.
Category / Program:	General Schedule
PBS Indication:	Hypercholesterolaemia
Restriction:	Authority required – in writing
Clinical criteria:	The treatment must be in conjunction with dietary therapy and exercise AND

	Patient must have symptomatic coronary heart disease; OR Patient must have symptomatic cerebrovascular disease; OR Patient must have symptomatic peripheral vascular disease. AND Patient must have an LDL-c cholesterol level in excess of 3.3 millimoles per litre after at least 3 months of treatment at a maximum tolerated dose of an HMG CoA reductase inhibitor (statin), in conjunction with dietary therapy and exercise; OR Patient must have an LDL-c cholesterol level in excess of 3.3 millimoles per litre after having developed a clinically important product-related adverse event during treatment with an HMG CoA reductase inhibitor (statin) necessitating a withdrawal of statin treatment; OR Patient must have an LDL-c cholesterol level in excess of 3.3 millimoles per litre and must be one in whom treatment with an HMG CoA reductase inhibitor (statin) is contraindicated.

2.3 The LDL-c thresholds included in the proposed restrictions were poorly justified and were not consistent with the available clinical evidence, treatment guidelines or current restrictions for ezetimibe. The PSCR (p3) stated the proposed higher eligibility thresholds for evolocumab than for ezetimibe is to target treatment with this more expensive agent to patients requiring reductions in LDL-c of the order of 50% or more to achieve target levels. The ESC also noted a potential gap exists for individuals who fail to achieve target LDL-c on maximum tolerated dose statin, but who are not eligible for evolocumab. The PBAC considered the proposed LDL-c thresholds for FH were reasonable, but defining the non-FH population with ASCVD would require further justification.

2.4 The full restrictions also include treatment criteria identifying patients with statin intolerance. However, intolerance to statins is common and poorly defined in clinical practice. The availability of a new and effective medicine may have the potential to broaden the definition of 'statin intolerance' in practice. Additionally, it is possible that physicians may not titrate to maximal tolerated dose with statins (with or without ezetimibe) if there is another effective add-on therapy available. The ESC considered that true statin intolerance is likely to be <5% of the eligible population and that a substantial nocebo effect likely exists. This can lead to the potential for substantial leakage into a population that is not truly statin intolerant. The PBAC noted the recent post-market review of ezetimibe showed an 18-53% usage of ezetimibe outside the intended population and that much of this use occurred in a population that was not up titrated to maximal tolerated statin dose, or where evidence of true statin intolerance was not demonstrated. The PBAC considered the definitions of "maximum tolerated dose" of a statin and "clinically important product-related adverse event" in the restriction requires revision to ensure that patients are treated with the maximal tolerated dose of statin.

2.5 The ESC agreed with the submission proposal to restrict prescribing to Consultant Physicians, consistent with the current evolocumab PBS listing.

2.6 The current listing of evolocumab is subject to a special pricing arrangement ([redacted]% rebate on government expenditure). The resubmission proposed a revision of the

special pricing arrangement to include a further discount for the expanded listing ([redacted]% rebate on government expenditure).

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

3 Background

Registration status

3.1 Evolocumab was approved by the TGA on 4 December 2015 for the treatment of:

- Adults with heterozygous familial hypercholesterolaemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD):
  - 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.

At the time of PBAC consideration, the current TGA indication notes that the effect of evolocumab on cardiovascular morbidity and mortality has not yet been determined.

3.2 The resubmission noted that the sponsor is seeking a revision of the TGA indication to include a broader population (any patient with hypercholesterolaemia OR atherosclerotic cardiovascular disease OR at risk of atherosclerotic cardiovascular disease) based on the availability of cardiovascular outcome data. The sponsor is also requesting TGA approval for evolocumab as a monotherapy agent. The proposed revision is expected to be considered by the TGA in August 2018.

Previous PBAC consideration

3.3 The outstanding matters of concerns from the previous March 2016 PBAC meeting are summarised in the table below.

Table 2: Outstanding matters of concern from March 2016 resubmission

Component	Matter of concern	How the resubmission addresses it
Clinical/ Economic issue	[6.34] The current published literature supports the hypothesis that a reduction in LDL-c levels is associated with a reduction in cardiovascular risk. Therefore the greater LDL-c 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.	The resubmission presented cardiovascular outcome data with evolocumab versus placebo from the key FOURIER trial.
Clinical issue	[6.3] Current data are inadequate to reliably inform the comparison of evolocumab and alirocumab.	The resubmission presented updated indirect analysis of evolocumab versus alirocumab with additional studies and subset populations (e.g. FH, inadequate control on statins).
Economic issue	[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.	The resubmission reduced complexity by removing the Framingham risk equations (with additional risk multipliers) and estimating cardiovascular risk (with additional risk multipliers) from alternative data sources/assumptions. The resubmission also reduced complexity by the removal of time dependent transitions when the time origin is not the start of the model ('tunnel states').
Economic issue	[6.47] Key issues with the economic model included the modelling of patient characteristics and the estimation of the underlying cardiovascular risk as well as the impact of these estimates on the transformation of LDL-c outcomes to cardiovascular outcomes. The issues had a moderate-to-high impact on the model and generally favoured evolocumab.	
Economic issue	[6.47] A key issue with the economic model was the assumption of perfect persistence.	The resubmission maintained this assumption but changed the structure of the model to allow testing of persistence rates in sensitivity analyses.
Economic issue	[7.6] The PBAC considered that the cost-effectiveness of evolocumab when used to treat heterozygous familial hypercholesterolaemia was unacceptably high and uncertain and that further clinical evidence for this population was required.	The resubmission acknowledged the limited available data in heterozygous FH but argued that the surrogate to final relationship between LDL-c and cardiovascular outcomes (supported by the FOURIER study) is generalisable to the target PBS populations.
Financial issue	[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, the proportion of patients eligible for treatment under the proposed restriction and likely treatment adherence in clinical practice.	The resubmission presented revised budget impact estimates based on data from additional sources. The resubmission stated that uncertainty can be managed through a risk share arrangement.

Source: Table 1.1-6 (p 20-21) of the resubmission

4 Population and disease

4.1 Hypercholesterolaemia is a condition characterised by elevated serum cholesterol levels and is associated with the development of atherosclerosis and an increased incidence of angina, myocardial infarction, stroke, coronary artery disease and peripheral vascular disease.

4.2 The target population in the resubmission is the subset of hypercholesterolaemia patients with high risk of cardiovascular events due to FH with very high LDL-c levels (> 5.0 mmol/L) OR non-FH with established ASCVD and high LDL-c levels (> 3.3 mmol/L) despite maximal tolerated dose of statins.

4.3 The resubmission claimed that evolocumab would replace or be used in addition to other non-statin therapies for hypercholesterolaemia.

5 Comparator

5.1 The resubmission nominated both ezetimibe (most widely used non-statin therapy) and placebo as the main comparators. The PBAC considered this was appropriate.

5.2 The resubmission also nominated alirocumab as a near market comparator on the basis that it is a similar agent to evolocumab (same drug class) with overlapping indications. The PBAC considered this nomination was appropriate.

5.3 Other non-statin therapies could also be relevant secondary comparators (fibrates, bile acid sequestrants, nicotinic acid derivatives) particularly in high risk populations such as the proposed PBS population which require intensive lipid management and therefore may need multiple therapeutic agents. However, the ESC noted that non-statin therapies, other than ezetimibe in combination with statins, have not been shown to result in a reduction of cardiovascular events. The PBAC agreed the nominated comparators were the most relevant for assessment of cost-effectiveness of evolocumab.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The sponsor clarified that the FH population had the highest unmet clinical need and acknowledged that further work may be required to establish the most cost-effective approach to make PCSK9 inhibitors available in the larger non-FH population. The clinician presented the clinical argument for the plausibility of the intermediate outcomes of reduced myocardial infarction (MI) and stroke leading to better survival, despite lack of CV mortality benefits in the FOURIER trial, and that a [redacted] year lag in achieving a CV mortality benefit has been seen in previous statin studies and is more biologically plausible. The clinician further argued that due to the higher risk of CV events, the FH population are very compliant with statin therapy and the requirement in the restriction to have had at least three months treatment with a maximum tolerated dose of a statin was reasonable and would not require further qualification. In response to the PBAC query about the appropriate LDL-c threshold for defining eligibility for treatment, the clinician stated that the requirement for >5 mmol/L in the absence of a prior CV event was reasonable and reflects patients who will present regularly with complications who may achieve a clinically meaningful reduction with a PCSK9 inhibitor and statin combination. The clinician also felt that

>3.3 mmol/L is appropriate for those who have established ASCVD. The PBAC considered that the hearing was informative.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (18), health care professionals (2) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described the high clinical need for patients, both with and without FH, who require effective therapies to lower LDL-c to less than 1.8 mmol/L. Several comments described evolocumab as a safe and effective alternative to statin therapy, to which they are intolerant.

Clinical trials

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

- One head-to-head comparison of cardiovascular outcomes with evolocumab versus placebo in hypercholesterolaemia patients with atherosclerotic cardiovascular disease (FOURIER) including an additional safety sub-study investigating neurocognitive effects (EBBINGHAUS). Data from the FOURIER/EBBINGHAUS trial have not previously been considered by the PBAC.
- One head-to-head comparison of atherosclerotic plaque burden with evolocumab versus placebo in hypercholesterolaemia patients with evidence of coronary disease (GLAGOV). Data from the GLAGOV trial have not previously been considered by the PBAC.
- Direct comparison of lipid outcomes with evolocumab versus placebo or ezetimibe in various hypercholesterolaemia populations (FOURIER, GLAGOV, GAUSS-2, GAUSS-3, RUTHERFORD-2, LAPLACE-2, MENDEL-2, DESCARTES). Lipid outcomes from FOURIER, GLAGOV, and GAUSS-3 trials have not previously been considered by the PBAC.
- Indirect comparison of lipid outcomes with evolocumab versus alirocumab in various hypercholesterolaemia populations (GAUSS-2, LAPLACE-1, LAPLACE-2, MENDEL-1, MENDEL-2, RUTHERFORD-2, YUKAWA-1, YUKAWA-2, McKenney 2012, Roth 2012, Stein 2012, Teramoto 2016, ODYSSEY HIGH FH, ODYSSEY ALTERNATIVE, ODYSSEY LONGTERM, ODYSSEY CHOICE-1, ODYSSEY CHOICE-2, ODYSSEY COMBO-I, ODYSSEY COMBO-2, ODYSSEY FH-1, ODYSSEY FH-2, ODYSSEY MONO, ODYSSEY OPTIONS-1, ODYSSEY OPTIONS-2, ODYSSEY JAPAN). The indirect comparison included updated data and new analyses not previously considered by the PBAC.

6.4 Details of the trials presented in the resubmission are provided in the table below.

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Evolocumab clinical trials		
20080398	Amgen Clinical Study Report (2012). A Phase 1, Randomised, Double-blind, Placebo-controlled, Ascending	Internal study report

	Multiple-dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AMG 145 in Subjects with Hyperlipidemia on Stable Doses of a Statin Dias C et al (2012). Effects of AMG 145 on Low-Density Lipoprotein Cholesterol Levels Results From 2 Randomised, Double-Blind, Placebo-Controlled, Ascending-Dose Phase 1 Studies in Healthy Volunteers and Hypercholesterolemic Subjects on Statins.	Journal of the American College of Cardiology 60: 1888–1898
20101154 (MENDEL-1)	Amgen Clinical Study Report (2012). A Randomised, Placebo- and Ezetimibe-controlled, Dose-ranging Study to Evaluate Tolerability and Efficacy of AMG 145 on LDL-c-C in Hypercholesterolemic Subjects With a 10-year Framingham Risk Score of 10% or Less (MENDEL-1: Monoclonal antibody against PCSK9 to reduce Elevated LDL-c-C in subjects currently Not receiving Drug therapy for Easing Lipid levels) Koren M et al (2012). Efficacy, safety and tolerability of a monoclonal antibody to protein convertase subtilisin/kexin type 9 as monotherapy in patients with hypercholesterolaemia (MENDEL-1): a randomised, double-blind, placebo-controlled, phase 2 study.	Internal study report Lancet 380:1995–2006
20101155 (LAPLACE-1)	Amgen Clinical Study Report (2014). A Double-blind, Randomised, Placebo-controlled, Multicenter, Dose-ranging Study to Evaluate Tolerability and Efficacy of AMG 145 on LDL-c-C in Combination with HMG-CoA Reductase Inhibitors in Hypercholesterolemic Subjects (LAPLACE: LDL-c-C Assessment w/ PCSK9 monoclonaL Antibody inhibition Combined with statin thErapy) Giugliano R et al (2012). Efficacy, safety and tolerability of a monoclonal antibody to protein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study.	Internal study report Lancet 380: 2007–2017
20090158 (RUTHERFORD-1)	Amgen Clinical Study Report (2012). A Double-blind, Randomised, Placebo-controlled, Multicenter Study to Evaluate Tolerability and Efficacy of AMG 145 on LDL-c-C in Subjects with Heterozygous Familial hypercholesterolaemia Raal F et al (2012). Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolaemia: The reduction of LDL-c-C with PCSK9 inhibition in heterozygous familial hypercholesterolaemia disorder (RUTHERFORD) randomized trial	Internal study report Circulation 126: 2408–2417
20090159 (GAUSS-1)	Amgen Clinical Study Report (2012). A Randomised, Multicenter Study to Evaluate Tolerability and Efficacy of AMG 145 on LDL-c-C, Compared with Ezetimibe, in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor (GAUSS: Goal Achievement after Utilising an anti-PCSK9 antibody in Statin Intolerant Subjects) Sullivan D et al (2012). Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: The GAUSS randomized trial	Internal study report Journal of the American Medical Association 308: 2497–2506
20110231 (YUKAWA-1)	Amgen Clinical Study Report (2013). A Double-blind, Randomised, Placebo-controlled, Multicenter Study to Evaluate Tolerability and Efficacy of AMG 145 on LDL-c-C in	Internal study report

	Combination With Stable Statin Therapy in Japanese Subjects With hypercholesterolaemia and High Cardiovascular Risk Hirayama A et al (2014). Effects of evolocumab (AMG 145), a monoclonal antibody to PCSK9, in hypercholesterolemic, statin-treated japanese patients at high cardiovascular risk - Primary results from the phase 2 YUKAWA study	Circulation Journal 78: 1073–1082
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 Koren MJ et al (2014). Anti-PCSK9 monotherapy for hypercholesterolaemia: The MENDEL-2 randomized, controlled phase III clinical trial of evolocumab	Internal study report 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-C in Combination with Statin Therapy in Subjects with Primary hypercholesterolaemia and Mixed Dyslipidemia. Robinson JG et al (2014). Effect of evolocumab or ezetimibe added to moderate- Or high-intensity statin therapy on LDL-c-C lowering in patients with hypercholesterolaemia: The LAPLACE-2 randomized clinical trial	Internal study report Journal of the American Medical Association 311: 1870–1882
20110116 (GAUSS-2)	Amgen Clinical Study Report (2014). A Double-blind, Randomised, Multicenter Study to Evaluate Safety and Efficacy of AMG 145, Compared With Ezetimibe, in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor 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	Internal study report 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-C in subjects with heterozygous familial hypercholesterolaemia. Raal F et al (2015). PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial.	Internal study report 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-C in Hyperlipidemic Subjects Blom D et al (2014). A 52-week placebo-controlled trial of evolocumab in hyperlipidemia.	Internal study report New England Journal of Medicine 370:1809–1819
20120122 (YUKAWA-2)	Amgen Clinical Study Report (2013). A Double-blind, Randomised, Placebo-Controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of AMG 145 on LDL-c-C in Combination With Statin Therapy in Japanese Subjects With High Cardiovascular Risk and With Hyperlipidemia or Mixed Dyslipidemia Kiyosue et al (2016). A Phase 3 Study of Evolocumab (AMG	Internal study report American Journal of Cardiology 117:

	145) in Statin-Treated Japanese Patients at HighCardiovascular Risk	40–47
20120332 (GAUSS-3)	Amgen Clinical Study Report (2016). A Double-blind, Randomised, Multicenter Study to Evaluate the Safety and Efficacy of AMG 145, Compared With Ezetimibe, in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor Due to Muscle Related Side Effects	Internal study report
	Nissen SE et al (2016). Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance. The GAUSS-3 randomised clinical trial	Journal of the American Medical Association 315: 1580–1590
20110118 (FOURIER)	Amgen Clinical Study Report (2017). A Double-blind, Randomised, Placebo-controlled, Multicenter Study Assessing the Impact of Additional LDL-c-Cholesterol Reduction on Major Cardiovascular Events When AMG 145 is Used in Combination With Statin Therapy in Patients with Clinically Evident Cardiovascular Disease	Internal study report
	Sabatine MS et al (2017). Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease	New England Journal of Medicine 376: 1713-1722
20130385 (EBBINGHAUS)	Amgen Clinical Study Report (2017). A Double-Blind, Placebo Controlled, Multicenter Study to Assess the Effect of Evolocumab on Cognitive Function in Patients with Clinically Evident Cardiovascular Disease and Receiving Statin Background Lipid Lowering Therapy: A Study for Subjects Enrolled in the FOURIER (Study 20110118) Trial	Internal study report
	Giugliano et al (2017). Cognitive Function in a Randomized Trial of Evolocumab	New England Journal of Medicine 377: 633-643
20120153 (GLAGOV)	Amgen Clinical Study Report (2016). A Randomised, Multi-center, Placebo-controlled, Parallel Group Study to Determine the Effects of AMG 145 Treatment on Atherosclerotic Disease Burden As Measured By Intravascular Ultrasound in Subjects Undergoing Coronary Catheterisation	Internal study report
	Nicholls SJ et al (2016). Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients. The GLAGOV Randomised Clinical Trial	Journal of the American Medical Association 316: 2373-2384
Alirocumab clinical trials		
McKenney (2012)	McKenney JM et al (2012). Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolaemia receiving ongoing stable atorvastatin therapy.	Journal of the American College of Cardiology 59: 2344–2353
Stein (2012)	Stein EA et al (2012). Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial.	Lancet 380: 29–36
Roth (2012)	Roth EM et al (2012). Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolaemia.	New England Journal of Medicine 367: 1891–1900
Teramoto (2014)	Teramoto T et al (2014). Efficacy and safety of alirocumab in Japanese patients with hypercholesterolaemia on stable statin therapy: First data with the 75 mg every two weeks dose	Circulation 130: A13651 [abstract only]
ODYSSEY	Roth EM et al (2014). Monotherapy with the PCSK9 inhibitor	International Journal of Cardiology

MONO	alirocumab versus ezetimibe in patients with hypercholesterolaemia: results of a 24 week, double-blind, randomized Phase 3 trial.	176: 55–61
ODYSSEY COMBO I	Kereiakes D et al (2015). Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: The ODYSSEY COMBO I study	American Heart Journal 169: 906-915
ODYSSEY COMBO II	Cannon CP et al (2015). Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial	European Heart Journal 36: 1186–1194
ODYSSEY OPTIONS I	Bays H et al (2015). Alirocumab as Add-on To Atorvastatin Versus Other Lipid Treatment Strategies: ODYSSEY OPTIONS I Randomized Trial.	Journal of Clinical Endocrinology and Metabolism 100: 3140-3148
ODYSSEY OPTIONS II	Farnier M et al (2016). Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular-risk patients: The ODYSSEY OPTIONS II randomized trial	Atherosclerosis 244: 138-146
ODYSSEY ALTERNATIVE	Moriarty P et al (2015). Efficacy and safety of alirocumab versus ezetimibe in statin-intolerant patients, with a statin-re-challenge arm: The ODYSSEY ALTERNATIVE randomized trial.	Journal of Clinical Lipidology 9: 758-769
ODYSSEY FH I	Kastelein J et al (2015). ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia.	European Heart Journal 36: 2996-3003
ODYSSEY FH II	Kastelein J et al (2015). ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia.	European Heart Journal 36: 2996-3003
ODYSSEY FH HIGHRISK	Ginsberg HN et al (2016). Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial Hypercholesterolaemia and LDL-c-C of 160 mg/dl or Higher	Cardiovascular Drugs and Therapy 30: 473–483
ODYSSEY LONG TERM	Robinson JG et al (2015). Efficacy and safety of alirocumab in reducing lipids and cardiovascular events.	New England Journal of Medicine 372: 1489–1499
ODYSSEY CHOICE I	Roth EM et al (2016). A phase III randomized trial evaluating alirocumab 300 mg every 4 weeks as monotherapy or add-on to statin: ODYSSEY CHOICE I	Atherosclerosis 254: 254-262
ODYSSEY CHOICE II	Stroes E et al (2016). Efficacy and Safety of Alirocumab 150 mg Every 4 Weeks in Patients With Hypercholesterolaemia Not on Statin Therapy: The ODYSSEY CHOICE II Study	Journal of the American Heart Association 5: e003421
ODYSSEY OUTCOMES	Schwartz G et al (2014). Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: Rationale and design of the ODYSSEY Outcomes trial.	American Heart Journal 168: 682-689

Source: Table 2.2-1 (p 38-45) of the resubmission; Table 3 (p 10-14) Attachment 5 of the resubmission
Note: Only includes the main publications for each trial

6.5 The resubmission focused on new data from the FOURIER, EBBINGHAUS and GLAGOV trials. The key features of these studies are summarised in the table below.

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

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
FOURIER	27,564	MC, R, DB, PC Approximately 2 year duration	Low	Hypercholesterolaemia with atherosclerotic disease	Cardiovascular events, lipid parameters	Used to support relationship between LDL-c and cardiovascular events
EBBINGHAUS Sub-study	1,974	Nested sub-study of FOURIER	Low	Hypercholesterolaemia with atherosclerotic disease	Neurocognitive measures	Not used
GLAGOV	970	MC, R, DB, PC 78 week duration	Low	Hypercholesterolaemia with atherosclerotic disease	Intravascular imaging outcomes	Not used

Abbreviations: DB, double blind; LDL-c, low density lipoprotein cholesterol; MC, multi-centre; PC, placebo-controlled; R, randomised.
Source: Table 2.2-1 (p 39-46), Table 2.3-1 (p 47-48), Table 2.4-1 (p 49) of the resubmission

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

Comparative effectiveness

6.6 The previous March 2015 and March 2016 submissions presented exploratory analyses of cardiovascular safety data from the OSLER studies (long-term follow-up of patients previously enrolled in the evolocumab lipid trials). These analyses suggested a potential reduction in cardiovascular risk with evolocumab compared to standard of care.

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

Table 5: Key cardiovascular time to event analyses reported in the FOURIER trial

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

Abbreviations: CTTC, Cholesterol Treatment Trialists' Collaboration
Source: Table 2.5-1 (p 54-55) of the resubmission; Table 10-9 (p 138), Table 14-4.3.25 (p 342), Table 14-4.3.26 (p 343) of the FOURIER trial report; Table 2 (p 6) of the Sabatine (2017) publication

6.8 The ESC noted the primary composite outcomes for major adverse cardiac events (MACE) and extended MACE endpoints were positive in the FOURIER trial data.

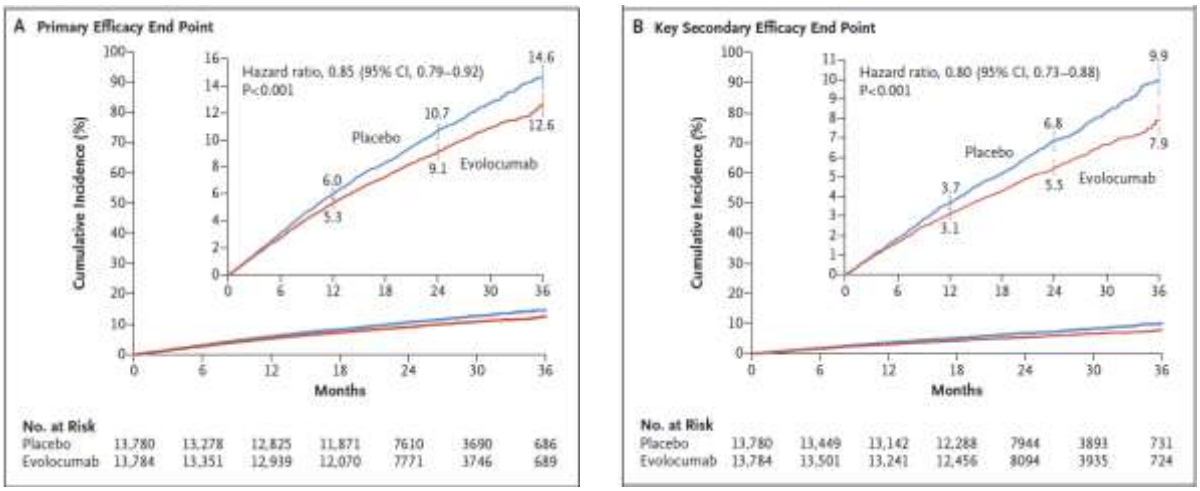
6.9 Treatment with evolocumab was associated with a decreased risk of myocardial infarction, coronary revascularisation and ischaemic stroke compared to placebo. There was no apparent difference in angina, coronary death, cardiovascular death or all-cause mortality between treatment arms, although ESC noted these were not individually primary or, for angina and coronary death, secondary endpoints. The difference in cardiovascular events was associated with a 59% relative decrease and a 1.38 mmol/L absolute decrease in LDL-c levels compared to placebo.

6.10 The results of the FOURIER trial were broadly consistent with the results from the IMPROVE-IT trial (the key cardiovascular outcome study for ezetimibe), noting that the entry criteria and clinical population studied in the two trials was different. Treatment with simvastatin and ezetimibe combination therapy was associated with a decreased risk of myocardial infarction (HR 0.87; 95% CI 0.80, 0.95), urgent coronary revascularisation (HR 0.81; 95% CI 0.72, 0.91) and ischaemic stroke (HR 0.79; 95% CI 0.67, 0.94) compared to simvastatin monotherapy. There was no apparent difference in angina, coronary death, cardiovascular death or all-cause mortality between

treatment arms. The difference in cardiovascular events was associated with an 18.3% relative decrease and a 0.33 mmol/L absolute decrease in LDL-c levels compared to simvastatin monotherapy.

6.11 A landmark analysis of FOURIER outcomes indicated that relative reductions in myocardial infarction, stroke and coronary revascularisations with evolocumab treatment were generally smaller in the first year compared to later years. There was no apparent difference in angina or mortality between treatment arms in the first year or subsequent years. The resubmission claimed that this analysis indicates that there is a treatment lag between the initiation of evolocumab therapy and the accrual of cardiovascular benefits. The resubmission also suggested that the Kaplan-Meier curves diverged with increasing duration of follow-up, as seen in Figures 1. The ESC noted, the economic model does not include a lag between treatment with evolocumab and CV events (see Economic analysis).

Figure 1: Cumulative Incidence of the primary and secondary endpoints in FOURIER



Primary end point consists of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary end point consists of cardiovascular death, myocardial infarction, or stroke.
Source: Figure 2.5-1 (p 55) of the resubmission

6.12 The FOURIER trial report noted some differences in treatment effects across patient subgroups defined by race, geographic location and previous history of myocardial infarction.

6.13 Cardiovascular imaging results from the GLAGOV trial indicated that treatment with evolocumab was also associated with a statistically significant reduction in atheroma volume over time compared to placebo (least squares mean change in percent atheroma volume -0.96 vs 0.05; treatment difference -1.01; 95% CI -1.38, -0.64).

6.14 A summary of LDL-c results from FOURIER, GLAGOV and the lipid trials demonstrated that treatment with evolocumab (fortnightly and monthly dosing) was associated with statistically significant decreases in LDL-c levels compared to ezetimibe (approximately 40% reduction) and placebo (approximately 60% reduction) in mixed hypercholesterolaemia populations. The LDL-c outcomes were consistent with results previously considered by PBAC (March 2015 and March 2016 evolocumab submissions).

6.15 An overall summary of the indirect analyses comparing evolocumab and alirocumab is summarised in the table below.

6.16 The inclusion/exclusion of trials for the indirect comparison was not adequately justified in the resubmission (e.g. comparisons include early phase II trials but do not include new data from the FOURIER trial).

6.17 The robustness of meta-analysed results used in the indirect analysis for both evolocumab and alirocumab was unclear given the major heterogeneity between studies (most I^2 estimates between 80-90%). Additionally, the exchangeability of the evolocumab and alirocumab trials was also unclear (varying study designs and trial characteristics).

6.18 The analyses presented in the resubmission do not directly address the comparative efficacy of evolocumab versus dose titration with alirocumab (recommended treatment regimen in the product information).

6.19 Alternative indirect analyses were also conducted during the evaluation comparing the results of the FOURIER trial (the most robust data for evolocumab) to the available alirocumab trials using placebo as the common comparator. Similar to the analyses presented in the resubmission, these analyses were limited by substantial heterogeneity in the alirocumab trials and uncertain exchangeability between the evolocumab and alirocumab trials.

Table 6: Indirect comparison of change in mean LDL-c levels with evolocumab and alirocumab in mixed hypercholesterolaemia populations

Comparison	Treatment difference, Mean (95% CI)
Evolocumab 140 mg versus alirocumab 75 mg (all trials) using placebo common comparator	**-17.30 (-24.56, -10.04)**
Evolocumab 140 mg versus alirocumab 75 mg (all trials) using ezetimibe common comparator	**-13.06 (-17.68, -8.44)**
Evolocumab 140 mg versus alirocumab 75 mg (inadequate control on statins) using placebo common comparator	**-20.25 (-28.60, -11.90)**
Evolocumab 140 mg versus alirocumab 75 mg (inadequate control on statins) using ezetimibe common comparator	**-19.52 (-27.39, -11.65)**
Evolocumab 140 mg versus alirocumab 75 mg (familial hypercholesterolaemia) using placebo common comparator	**-11.70 (-18.82, -4.58)**
Evolocumab 140 mg versus alirocumab 75 mg (statin intolerant) using ezetimibe common comparator	-7.78 (-15.56, 0.00)
Evolocumab 140 mg versus alirocumab 150 mg (all trials) using placebo common comparator	**-10.60 (-19.07, -2.13)**
Evolocumab 140 mg versus alirocumab 150 mg (familial hypercholesterolaemia) using placebo common comparator	-12.35 (-30.00, 5.30)
Evolocumab 140 mg versus alirocumab 150 mg (inadequate control on statins) using placebo common comparator	**-13.93 (-23.42, -4.44)**
Evolocumab 420 mg versus alirocumab 300 mg (all trials) using placebo common comparator	**-13.62 (-23.56, -3.68)**
Evolocumab 420 mg versus alirocumab 300 mg (familial hypercholesterolaemia) using placebo common comparator	**-31.22 (-46.96, -15.48)**
Evolocumab 420 mg versus alirocumab 300 mg (inadequate control on statins) using placebo common comparator	-8.12 (-16.97, 0.73)
Evolocumab 140 or 420 mg (FOURIER) versus alirocumab 75 mg (all trials) using placebo common comparator	**-6.30 (-11.34, -1.26)**
Evolocumab 140 or 420 mg (FOURIER) versus alirocumab 150 mg (all trials) using placebo common comparator	0.40 (-6.27, 7.07)
Evolocumab 140 or 420 mg (FOURIER) versus alirocumab titration 75-150 mg (all trials) using placebo common comparator	**-4.43 (-9.54, 0.68)**
Evolocumab 140 or 420 mg (FOURIER) versus alirocumab 300 mg (all trials) using placebo common comparator	**-9.90 (-19.32, -0.48)**

Abbreviations: CI, confidence interval

Source: Table 15 (p 38-40), Table 16 (p 41-45); Figure 7 (p 51); Figure 10 (p 53); Figure 11 (p 54), Figure 13 (p 56), Figure 15 (p 57), Figure 16 (p 58), Figure 17 (p 59); Figure 19 (p 60); Figure 20 (p 61) of Attachment 5 of the resubmission; Table 14-4.15.1 (p 576) of the FOURIER trial report.

Note: Resubmission only presented p-values for indirect analyses. Mean treatment difference was calculated during the evaluation based on Bucher method using Excel workbook published by Tobias et al [IMTC.xls; Version 1.0.1, October 2013] available at http://metaanalisisenred.weebly.com/excel.html.

6.20 Indirect analyses conducted in the resubmission indicated that treatment with evolocumab was associated with a statistically significantly larger reduction in LDL-c levels compared to alirocumab for all dose strengths.

6.21 Indirect analyses conducted during the evaluation indicated the treatment with evolocumab was associated with a statistically significantly larger reduction in LDL-c levels compared to lower-dose alirocumab treatment regimens (75 mg fortnightly, 300 mg monthly). However, there was no statistically significant difference between evolocumab and higher dose alirocumab treatment regimens (150 mg fortnightly, titration 75-150 mg fortnightly). The PSCR (p2) agreed with the conclusion in the Commentary.

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

Comparative harms

6.22 The incidence of adverse events reported in new evolocumab trials was consistent with previous data.

6.23 The most frequently reported adverse events with evolocumab were musculoskeletal disorders (myalgia, pain in extremity, muscle spasms, arthralgia, back pain), infections (nasopharyngitis, upper respiratory tract infection, influenza), general disorders and administration site conditions (fatigue, injection site reactions), gastrointestinal disorders (diarrhoea, nausea, constipation) and nervous system disorders (headache).

6.24 In regards to adverse events of special interest, treatment with evolocumab was associated with a higher incidence of mild to moderate hypersensitivity reactions and injection site reactions compared to placebo.

6.25 There was no statistically significant difference in neurocognitive measures between evolocumab and placebo for patients enrolled in the EBBINGHAUS sub-study.

6.26 Available comparative safety data did not clearly favour evolocumab, ezetimibe or placebo. There was insufficient data presented in the resubmission to adequately assess the comparative safety of evolocumab and alirocumab.

6.27 An expanded assessment of harms did not identify any important risk with evolocumab treatment. Important potential risks included hypersensitivity reactions and immunogenicity (i.e. development of anti-evolocumab antibodies). Missing information for evolocumab included the long-term effects of exposure to low LDL-c levels (< 1 mmol/L).

6.28 The ESC noted the development of anti-evolocumab antibodies was detected in 0.3% (43/13,789) of patients. The presence of anti-evolocumab antibodies was not associated with a reduction in treatment efficacy or an increase in the incidence of adverse events.

6.29 While there is limited (4 year+) long-term safety data, no safety signals have been identified in the new data submitted or in the PSUR and there are no safety signals for very low LDL-c levels (<0.6mmol/L), particularly neurocognitive.

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

Benefits and harms

6.30 On the basis of direct evidence presented in the resubmission, for every 1000 patients (hypercholesterolaemia with atherosclerotic disease) treated with evolocumab in comparison to placebo would result in:

- Approximately 12 fewer patients with myocardial infarction over a mean duration of 2 years
- Approximately 4 fewer patients with ischaemic stroke over a mean duration of 2 years
- Approximately 15 fewer patients with coronary revascularisation over a mean duration of 2 years
- No apparent difference in cardiovascular death over a mean duration of 2 years
- No apparent difference in adverse events over a mean duration of 2 years

6.31 On the basis of direct evidence presented in the resubmission, the comparison of evolocumab and placebo in patients with hypercholesterolaemia resulted in:

- Approximately a 60% relative reduction in LDL-c levels
- No apparent difference in adverse events

6.32 On the basis of direct evidence presented in the resubmission, the comparison of evolocumab and ezetimibe in patients with hypercholesterolaemia resulted in:

- Approximately a 40% relative reduction in LDL-c levels
- No apparent difference in adverse events

6.33 Current data are inadequate to reliably quantify the comparative benefits and harms of evolocumab and alirocumab.

Interpretation of clinical evidence

6.34 The resubmission described evolocumab as superior in terms of efficacy (based on surrogate outcome measures) and similar in terms of safety compared to ezetimibe. The PBAC considered this claim is reasonable based on the direct comparison on data from the evolocumab lipid trials.

6.35 The resubmission described evolocumab as superior in terms of efficacy and similar in terms of safety compared to placebo. This claim is reasonable based on the direct comparison of treatments in the FOURIER trial (although evolocumab was not associated with a reduction in cardiovascular mortality). The PBAC noted the FOURIER trial was not powered to show a mortality benefit, it was not a primary or secondary endpoint in the trial and the follow-up period was likely too short. Effect on all of the other cardiovascular outcomes was robust and consistent with the extensive body of knowledge of the benefits of LDL-c lowering.

6.36 The resubmission described evolocumab as superior in terms of efficacy (based on surrogate outcome measures) and similar in terms of safety compared to alirocumab. The ESC considered the efficacy claim may be reasonable against lower

dose strengths of alirocumab (75 mg fortnightly or 300 mg monthly) but was not adequately supported for higher strengths (titration 75-150 mg fortnightly, 150 mg fortnightly). The safety claim may also be reasonable despite the lack of comparative data. The PBAC noted the 75 mg fortnightly dose is titratable to 150 mg fortnightly; a dose for which the superiority claim is not supported.

6.37 The PBAC considered that the claim of superior comparative effectiveness compared to ezetimibe (based on the lipid trials) and placebo (based on the FOURIER trial) was reasonable.

6.38 The PBAC considered that the claim of similar safety compared to ezetimibe (based on the lipid trials) and placebo (based on the FOURIER trial) was reasonable.

6.39 The PBAC considered the comparative efficacy and safety to alirocumab remains uncertain.

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

Economic analysis

6.40 The resubmission presented a stepped economic evaluation of evolocumab for the treatment of familial hypercholesterolaemia with atherosclerotic disease, familial hypercholesterolaemia with very high LDL-c levels and non-familial hypercholesterolaemia with atherosclerotic disease either as a replacement to ezetimibe or as an add-on to existing therapies.

6.41 The economic evaluation was based on relative LDL-c reductions from the clinical trials and other modelled variables. The resubmission did not use cardiovascular outcome data from the FOURIER trial in the economic evaluation.

Table 7: Key components of the economic evaluation

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

Abbreviations: CHD, coronary heart disease; LDL-c, low density lipoprotein cholesterol; MI, myocardial infarction
Source: Table 3.1-1 (p 78) of the resubmission

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

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

Table 8: Key drivers of the model

Description	Method/Value	Impact
Treatment effect on coronary death	The resubmission assumed a reduction in coronary death with active treatments based on a multistep transformation of lipid parameters: - Relative LDL-c reductions translated to absolute reductions based on assumed baseline LDL-c levels -Transformed LDL-c reductions translated to relative reductions in cardiovascular risk based on the CTTC analysis (RR 0.78 per 1 mmol/L reduction in LDL-c) - Relative reductions in cardiovascular risk translated to absolute reductions based on assumed baseline risk levels Based on this transformation the resubmission estimated a substantial reduction in coronary mortality with evolocumab treatment (approximately 55-64% risk reduction) and a smaller reduction in coronary mortality with ezetimibe (approximately 22-27% risk reduction). This estimate was inconsistent with the results of the FOURIER trial which did not demonstrate a statistically significant difference in coronary death between evolocumab and placebo (HR 1.02; 95% CI 0.82, 1.25). The modelled reduction in coronary death was the primary driver of the economic model. The ESC considered a long term reduction in CV death to be reasonable, however the 55-64% risk reduction with evolocumab may be overstated. This risk reduction was not validated with external data. The resubmission argued a time lag between LDL-c reductions and the impact on cardiovascular risk was not incorporated into the economic model because it was noted that the PBS Statin Review did not model a time lag. The ESC considered the clear separation of cardiovascular death rates associated with evolocumab treatment compared to placebo and ezetimibe within the first year of the model was inconsistent with the FOURIER trial evidence.	Very high, favours evolocumab
Baseline cardiovascular risk	The resubmission assumed a cardiovascular event rate of 0.05 events per subject year (equivalent to a 5-year risk of 23%) in non-familial hypercholesterolaemia with atherosclerotic disease. The resubmission assumed that familial hypercholesterolaemia with very high LDL-c levels (LDL-c > 5.0 mmol/L) would have the same cardiovascular events rate as non-familial hypercholesterolaemia with atherosclerotic disease (0.05 events per subject year). The resubmission assumed that familial hypercholesterolaemia with atherosclerotic disease (LDL-c > 3.3 mmol/L) would have twice the event rate of non-familial hypercholesterolaemia with atherosclerotic disease (0.10 events per subject year). The baseline risk assumptions were broadly based on cardiovascular risk estimates in untreated hypercholesterolaemia populations and epidemiology estimates of the increased risk associated with familial hypercholesterolaemia. The ESC agreed that familial hypercholesterolaemia was associated with an increased cardiovascular risk for any given cholesterol level than the general ASCVD population, but considered there were insufficient data presented in the submission to adequately support the assumptions regarding baseline cardiovascular risk and therefore it was unclear whether they were representative	High, favours evolocumab

Description	Method/Value	Impact
	of the target PBS populations.	
Baseline LDL-c levels	The resubmission assumed that the LDL-c eligibility criterion (> 3.3 mmol/L) for PBS populations with atherosclerotic disease would result in a mean baseline LDL-c level of 5.5 mmol/L. The resubmission assumed that the LDL-c eligibility criterion (> 5 mmol/L) for PBS populations without atherosclerotic disease would result in a mean baseline LDL-c level of 7.0 mmol/L. The baseline LDL-c assumptions were not justified in the resubmission and therefore it was unclear whether they were representative of the target PBS populations.	High, favours evolocumab
Distribution of cardiac events	The resubmission estimated the distribution of cardiac events (myocardial infarction: 38.8%; ischaemic stroke 27.7%; coronary death 34.5%) based on the Heart Protection Study. The Heart Protection Study is unlikely to be representative of the target PBS populations. The most closely comparable distribution of events reported in the FOURIER trial for the placebo arm was: myocardial infarction: 62.0%, stroke: 23.5%, cardiovascular death 14.5%. The ESC noted these modelled CV events did not match the CTTC composite outcome for which the events were predicated upon (coronary death, MI, ischaemic and haemorrhagic stroke, coronary revascularisation). A more appropriate approach would be to use individual CV event and mortality equations, which are reported in the FOURIER trial.	High, favours evolocumab
Time horizon	The economic model was based on a 35 year time horizon. The nominated time horizon appeared appropriate to capture the majority of costs and benefits in patients with atherosclerotic disease but may be insufficient for familial patients with very high LDL-c levels (baseline age 45 years; approximately 20-40% of patients were alive at the end of the model).	High, variable direction

Abbreviations: CTTC, Cholesterol Treatment Trialists' Collaboration; LDL-c, low density lipoprotein cholesterol; PBS, Pharmaceutical Benefits Scheme
Source: compiled during the evaluation

6.44 The results of the modelled economic evaluation are summarised below.

Table 9: Summary results of stepped economic evaluation of evolocumab versus ezetimibe or placebo

Type of resource item	Evolocumab	Ezetimibe	Placebo	Increment vs	
				Ezetimibe	Placebo
Familial hypercholesterolaemia with atherosclerotic disease					
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	8.106	6.907	6.300	1.199	1.807
Incremental cost per QALY gained				[redacted]	[redacted]
Familial hypercholesterolaemia with very high LDL-c					
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	11.553	10.026	9.154	1.528	2.399
Incremental cost per QALY gained				[redacted]	[redacted]
Non-familial hypercholesterolaemia with atherosclerotic disease					
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	9.209	8.361	7.883	0.848	1.326
Incremental cost per QALY gained				[redacted]	[redacted]

Abbreviations: QALYs, quality-adjusted life years
Source: Constructed during the evaluation based on data from the 'Evolocumab Model Nov17' Excel workbook

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

$45,000/QALY - $75,000/QALY, for familial hypercholesterolaemia with atherosclerotic disease, $15,000/QALY - $45,000/QALY and familial hypercholesterolaemia with very high LDL-c, and $15,000/QALY - $45,000/QALY and $45,000/QALY - $75,000/QALY for non-familial hypercholesterolaemia with atherosclerotic disease.

6.45 The modelled baseline LDL-c cholesterol level, the modelled cardiovascular event rate, the modelled distribution of cardiac events and the extrapolation of the modelled time horizon to 35 years had the largest impact on the stepped economic evaluation.

6.46 The results of sensitivity analyses conducted during the evaluation indicated that the model was most sensitive to the assumed reduction in coronary death associated with LDL-c lowering. Neither evolocumab nor ezetimibe have demonstrated a reduction in cardiovascular death.

Table 10: Summary results of sensitivity analyses removing coronary death treatment effects

Type of resource item	Evolocumab	Ezetimibe	Placebo	Increment vs	
				Ezetimibe	Placebo
Familial hypercholesterolaemia with atherosclerotic disease (no coronary death treatment effect)					
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	6.597	6.406	6.288	0.191	0.309
Incremental cost per QALY gained				[redacted]	[redacted]
Familial hypercholesterolaemia with very high LDL-c (no coronary death treatment effect)					
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	9.550	9.312	9.149	0.238	0.401
Incremental cost per QALY gained				[redacted]	[redacted]
Non-familial hypercholesterolaemia with atherosclerotic disease (no coronary death treatment effect)					
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	8.108	7.966	7.876	0.142	0.232
Incremental cost per QALY gained				[redacted]	[redacted]

Abbreviations: QALYs, quality-adjusted life years
Source: Constructed during the evaluation based on data from the 'Evolocumab Model Nov17' Excel workbook

The redacted table shows ICERs in the range of $105,000/QALY - $200,000/QALY, for familial hypercholesterolaemia with atherosclerotic disease and familial hypercholesterolaemia with very high LDL-c, and more than $200,000/QALY for non-familial hypercholesterolaemia with atherosclerotic disease after removing coronary death treatment effects.

6.47 The results of the sensitivity analyses indicate that treatment with evolocumab was associated with very high incremental cost-effectiveness ratios if no mortality benefit was assumed. This may represent an overly conservative assumption given the clear reductions in myocardial infarction and ischaemic stroke associated with evolocumab treatment and the reduction of mortality seen in the statin meta-analyses. However, the structure of the economic model did not easily allow investigation of other alternatives such as a delayed impact on mortality or only having mortality reduction directly linked to myocardial infarctions and ischaemic stroke (approaches which have been used in other published economic models).

6.48 The PBAC noted the pre-PBAC response (p1) provided sensitivity analyses incorporating a [redacted] year time lag in CV mortality benefit for the FH population with ASCVD, with resultant ICERs of $15,000/QALY - $45,000/QALY gained , up from $15,000/QALY - $45,000/QALY gained in the base case.

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

Drug cost/patient/year: $[redacted]

6.49 The estimated drug cost for evolocumab per patient per year was $[redacted] (based on 13 scripts using the effective DPMQ $[redacted] for the 140 mg fortnightly injection).

6.50 The estimated drug cost for ezetimibe per patient per year was $802 (based on 12 scripts, using the current DPMQ $66.84 for ezetimibe 10 mg tablets).

Estimated PBS usage & financial implications

6.51 This resubmission was considered by DUSC. The resubmission used epidemiological (FH with ASCVD, FH with very high LDL-c) and market share (non-FH with ASCVD) approaches to estimate the utilisation/financial implications associated with the PBS listing of evolocumab.

Table 11: Estimated utilisation and cost to the PBS of evolocumab in the first six years of listing (effective price less patient copayments and cost offsets for change in use of background therapies)

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Year 6 (2023)
Familial hypercholesterolaemia with atherosclerotic disease						
Treated patients	[redacted]					
Estimated 140 mg scripts	[redacted]					
Estimated 420 mg scripts	[redacted]					
Total cost (effective price)	[redacted]					
Patient co-payments	[redacted]					
Substitution cost-offsets	[redacted]					
Net cost	[redacted]					
Familial hypercholesterolaemia with very high LDL levels						
Treated patients	[redacted]					
Estimated 140 mg scripts	[redacted]					
Estimated 420 mg scripts	[redacted]					
Total cost (effective price)	[redacted]					
Patient co-payments	[redacted]					
Substitution cost-offsets	[redacted]					
Net cost	[redacted]					
Non-familial hypercholesterolaemia with atherosclerotic disease						
Treated patients	[redacted]					
Estimated 140 mg scripts	[redacted]					
Estimated 420 mg scripts	[redacted]					
Total cost	[redacted]					

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Year 6 (2023)
(effective price)						
Patient co-payments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Substitution cost-offsets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FH, familial hypercholesterolaemia; ASCVD, atherosclerotic cardiovascular disease
Source: Table 4.4-1 (p 138) of the resubmission

The redacted table shows that at year 5, for familial hypercholesterolaemia with atherosclerotic disease, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be $20 - $30 million per year.

The redacted table shows that at year 5, for familial hypercholesterolaemia with very high LDL levels, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be $10 - $20 million per year.

The redacted table shows that at year 5, for non-familial hypercholesterolaemia with atherosclerotic disease, the estimated number of patients was 50,000 – 100,000 per year and the net cost to the PBS would be more than $100 million per year.

6.52 The estimated cumulative net cost across all populations was more than $100 million per year over six years (published price more than $100 million).

6.53 The DUSC considers the eligible population with FH and ASCVD presented in the submission to be underestimated, but uptake of evolocumab to be substantially overestimated. The number of patients with non-familial ASCVD are highly uncertain. The main issues are:

- The number of patients with FH and symptomatic ASCVD are likely to be underestimated because
  - An adjustment for increased detection of FH is reasonable but should not have been applied to the proportion of patients with symptomatic disease who are presumably diagnosed. The pre-PBAC response (p2) suggested the assumption of prior diagnosis may not be correct and that the current diagnosis rate is low due to the complexity of the Dutch Lipid Clinical Network Score and the implications of diagnosis, and the expense of genetic testing; and
  - The proportion of the FH population with clinical disease can be determined from the AusDiab study but should have been applied to the adult rather than the overall Australian population.
- Estimating the size of the population with non-FH and ASCVD is difficult and the budget impact is highly uncertain. The DUSC agreed that the availability of evolocumab may result in growth in the market but the magnitude of this growth is unclear. People on lipid lowering therapies other than ezetimibe may be eligible for evolocumab and may not have been adequately accounted for in the estimates.
- The uptake of evolocumab in the eligible population (40% in Year 1 increasing to 70% for FH and ASCVD; 20% increasing to 50% for FH primary prevention, 25% increasing to 50% for non-FH and ASCVD) is an overestimate based on uptake of injectable therapies

in other chronic disease markets such as diabetes and osteoporosis. In the pre-PBAC response, the sponsor considered that the particular characteristics that the medicine has relative to its alternatives (rather than the route of administration) may be the most important factor in uptake.

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

Quality use of medicines

6.54 The resubmission claimed that the requested Authority Required restriction would reduce the risk of inappropriate use. The resubmission also stated that the sponsor provides a number of education tools for clinicians to assist in identifying eligible patients and provides financial support for the maintenance of a national familial hypercholesterolaemia registry. A patient support program for evolocumab was also commenced in 2016 and includes information about evolocumab and an injection reminder service.

6.55 It is unclear whether the requested restriction (authority level, clinical criteria for statin intolerance) and other proposed activities adequately address quality use of medicine issues surrounding statin intolerance (identification of intolerance, early use of second-line therapies before optimal statin titration).

6.56 The DUSC noted the population with CVD is not homogenous. The submission did not consider QUM initiatives for the populations with the highest burden of CVD including Aboriginal and Torres Strait Islanders and those with mental illness.

Financial management – risk sharing arrangements

6.57 The current listing of evolocumab is subject to a risk sharing arrangement (subsidisation cap). The resubmission states that the sponsor is willing to consider a revised risk share arrangement for evolocumab which reflects forecast utilisation under the recommended restrictions and which will provide certainty as to the absolute maximum cost of evolocumab to the PBS.

6.58 The current listing of evolocumab is subject to a special pricing arrangement ([redacted]% rebate on government expenditure). The resubmission proposed a revision of the special pricing arrangement to include a further discount for the expanded listing ([redacted]% rebate on government expenditure).

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

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation to extend the PBS listing of evolocumab for patients with familial hypercholesterolaemia in order to address the residual uncertainty with the economic model following revisions provided in the pre-PBAC response. The PBAC did not recommend the listing of evolocumab for patients with non-familial hypercholesterolaemia with atherosclerotic disease on the basis of a high incremental cost effectiveness ratio and high and uncertain patient population numbers.

Familial hypercholesterolaemia (FH)

7.2 The PBAC noted the high unmet clinical need for additional effective therapy for patients with FH, recognising the increased risk of CV events for the FH population is not captured in risk calculators based on LDL-c. The PBAC considered that optimal dosing and up titration of statins remains a major QUM issue, however the committee noted the sponsor hearing emphasised that for the FH population at elevated risk of CV events, it is not in patients' interest to discontinue use of statins and/or ezetimibe or to not uptitrate statins as required to attain target LDL-c levels.

7.3 The PBAC noted the proposed Authority Required (written) restriction was complex as there are multiple considerations required to define a potentially cost-effective population.

- The proposed reduction in the Dutch Lipid Clinic Network Score from at least 7 (in the current homozygous FH PBS listing) to at least 6 (for a broader listing that includes both homozygous and heterozygous FH) appears reasonable, as the PBAC noted a score of 6–8 is considered probable FH.
- The PBAC noted the proposed LDL-c qualifying thresholds of $\geq$ 3.3 mmol/L in FH patients with ASCVD and $\geq$ 5.0 mmol/L in FH patients without ASCVD differ to the PBS listing for ezetimibe (which specifies a total cholesterol (TC) qualifying threshold of > 4.0 mmol/L in patients with and without ASCVD) and are not consistent with the clinical trial evidence which generally used less restrictive LDL-c thresholds. The PBAC considered the proposed thresholds in this submission may be reasonable, as suggested in the sponsor hearing. These thresholds would allow for meeting treatment goals of a reduction in LDL-c by >50% and/or reaching a primary prevention target of < 2.5 mmol/L for FH patients without ASCVD and a secondary prevention target of < 1.8 mmol/L for FH patients with ASCVD.
- The PBAC noted symptomatic ASCVD was not adequately defined in the restriction and considered that greater clarification and increased specificity of the eligible population to be important for targeting the most appropriate clinical and cost-effective population.
- The PBAC noted the sponsor hearing suggestion that FH patients are compliant with titrating statins to the maximum tolerated dose, however the Committee considered further treatment criteria to define statin intolerance was required, such as a requirement for rechallenging after a treatment break with a lower dose or alternative statin, as suggested by a number of reviews and guidelines.
- The PBAC also noted the proposed PBS listing would allow monotherapy with evolocumab in patients who are intolerant/contraindicated to statins and that this use is currently outside the approved TGA indication. The PBAC considered this to be a significant issue as many patients who are unable to tolerate statins are also unable to tolerate ezetimibe, and therefore monotherapy with a PCSK9 inhibitor would meet a high clinical need for a potentially substantial population. The Committee further considered the management of non-statin lipid-modifying treatment with evolocumab, and

the cost-effectiveness of this, required further consideration.

7.4 The PBAC considered the nominated comparators of ezetimibe and placebo to be appropriate. The secondary nomination of alirocumab as a near market comparator was also informative.

7.5 The PBAC acknowledged the cardiovascular outcomes data from the FOURIER trial addressed previous concerns regarding the lack of CV event data for evolocumab. The PBAC considered that while the trial did not demonstrate a reduction in mortality with evolocumab compared to placebo, the trial was not powered to show a mortality benefit, it was not a primary or secondary endpoint in the trial, and the follow-up period was too short. Effect on all other cardiovascular outcomes was robust and consistent with the extensive body of knowledge of the benefits of LDL-c lowering.

7.6 The PBAC noted that although the indirect analyses with alirocumab suggest that treatment with evolocumab was associated with a statistically significantly larger reduction in LDL-c levels compared to lower-dose alirocumab treatment regimens (75 mg fortnightly, 300 mg monthly), superiority to the recommend dose of 150 mg fortnightly was not shown. The PBAC noted the indirect comparisons were limited by substantial heterogeneity in the alirocumab trials and uncertain exchangeability between the evolocumab and alirocumab trials. The PBAC noted there will be a CV outcomes trial for alirocumab (ODYSSEY OUTCOMES) reporting in 2018, which may inform a comparison with the FOURIER trial.

7.7 The PBAC noted while a lack of long-term safety was previously a potential concern, in the 4 year+ data available there has been no evidence of a safety signal over neurocognitive function with very low LDL-c, gonadal and adrenal function, or transport of fat-soluble vitamins. The PBAC noted there is inadequate data to adequately assess comparative safety of evolocumab and alirocumab.

7.8 The PBAC noted concerns raised in the evaluation regarding the modelling of a reduction in cardiac death without trial data supporting any difference between evolocumab and placebo. The PBAC agreed with the ESC and the sponsor hearing that given the hard major adverse cardiac events (MACE) and extended MACE endpoints were unequivocally positive in the FORUIER trial data it is plausible that these differences would lead to better survival with longer follow-up. However, the PBAC considered a time lag between LDL-c reduction and the impact on cardiovascular risk should have been incorporated into the economic model. The PBAC noted the pre-PBAC response (p1) adjusted the model for FH patients with ASCVD to include [redacted]-year time lags in CV mortality benefit increasing the ICER from $15,000/QALY - $45,000/QALY gained in the base case to $15,000/QALY - $45,000/QALY gained for a [redacted]-year lag.

7.9 The PBAC considered the mortality benefit modelled remains optimistic with the [redacted]-year time lags, noting that only a small number of statin trials, which have an early treatment effect, showed mortality benefit at two years. The PBAC further noted the Amgen sponsored analysis by Fonarow (2017) modelled the treatment effect of evolocumab vs placebo with no improvement in cardiovascular death in the first 5 years of treatment. The PBAC expected cost-effectiveness for evolocumab should be achievable for the high need and well-defined FH populations

if a [redacted]-year time lag is incorporated, with a corresponding price adjustment to reflect this delayed mortality benefit.

7.10 The PBAC noted the difficulties in estimating the eligible FH population and uptake as outlined by the DUSC and considered revised financial estimates for the FH population only, including a reduced price, would need to address these concerns. The PBAC considered the cost-offsets for ezetimibe should be set to zero given best practice would be to use evolocumab in combination with ezetimibe and statins where possible, as was explained in the sponsor hearing. The PBAC also considered a new risk-share arrangement would need to incorporate a cap on financial estimates for PCSK9 inhibitors to account for potential use in the non-FH population.

7.11 The PBAC considered a resubmission should include the following:

- Restriction with more specific definitions of ASCVD and statin intolerance, and clarity that patients are required to be on other lipid lowering therapy/ies to be eligible for evolocumab
- Indirect comparison with alirocumab using the FOURIER trial and ODYSSEY OUTCOMES trial data, if available
- Revised base cases for both the FH with ASCVD and FH with very high LDL-c populations incorporating a time lag for CV mortality benefit of between [redacted] years and a reduced price to achieve comparable ICERs to those presented in this November 2017 submission
- Revised financial implications for the FH population only, including a risk-share arrangement with a cap to account for uncertainty on the size and uptake of the eligible FH population and potential use outside the approved FH population into the non-FH population.

Outcome:

Deferred

Non-Familial hypercholesterolaemia (non-FH) with atherosclerotic cardiovascular disease (ASCVD)

7.12 The PBAC acknowledged there is a high unmet clinical need for patients with non-FH and ASCVD who are not adequately controlled with available lipid-lowering therapies, but considered that this population was inadequately defined. The PBAC advised further modelling could be used to determine the qualifying LDL-c level for the non-FH population with ASCVD, and the proposed PBS restriction would require more specific definitions of ASCVD and statin intolerance.

7.13 The PBAC noted the pre-PBAC response (p1) suggested a stakeholder meeting to discuss the role of PCSK9 inhibitors in the wider population, however, the PBAC was reluctant to enter into such discussions without greater clarity and agreement about the non-FH population who would most benefit from PCSK9 inhibitors and without further economic modelling of the cost-effectiveness and opportunity cost of a broader listing upon which to base such discussions. The PBAC also noted that

outcome data for alirocumab is not yet available and would also be needed to inform such discussions.

7.14 The PBAC noted the FOURIER trial population was more aligned with the non-FH population with ASCVD and that these trial data could be used to better inform the economic model. As with the FH population, more conservative assumptions about the time to CV mortality benefit should be included in a future economic model.

7.15 The PBAC noted the very high financial impact of extending the listing beyond the FH population and noted the DUSC raised considerable uncertainty in the estimates and likelihood of growth in the market. The PBAC considered a risk-share arrangement to manage the financial risks, including hard caps with 100% rebates, would need to be considered.

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

Outcome:

Rejected

8 Context for Decision

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

9 Sponsor's Comment

Amgen is pleased that the PBAC has acknowledged the positive cardiovascular outcomes achieved in the FOURIER trial. Patients with familial hypercholesterolaemia are at very high CV risk and require access to effective therapy to achieve meaningful reductions in LDL-C. Amgen intends to work with PBAC to adjust the economic model as an immediate priority with the aim to extend the current PBS listing to include these patients.

Amgen will continue to work with PBAC towards achieving reimbursement for all patients in whom there is a clinical need.