

## 5.01 ALIROCUMAB, Injection 75 mg in 1 mL, single dose pre-filled pen, 2, Injection 150 mg in 1 mL, single dose pre-filled pen, 2, Praluent®, Sanofi-Aventis Australia Pty Ltd

### 1 Purpose of application

- 1.1 The submission requested a Section 85, Authority Required listing for alirocumab for treatment of heterozygous familial hypercholesterolaemia (HeFH) and clinical atherosclerotic cardiovascular disease (ASCVD) in patients with inadequate control on statins and statin-intolerant patients. The PBAC has not previously considered alirocumab.
- 1.2 The listing was requested on the basis of cost-effectiveness compared with ezetimibe and placebo.

**Table 1: Key components of the clinical issue addressed in the submission**

Component	Description
Population	Patients with HeFH with clinical ASCVD previously on a maximum tolerated dose of a statin or who are statin-intolerant and have not achieved target LDL-c levels
Intervention	Alirocumab 75 mg initially, titratable to 150 mg if further LDL-c lowering is required, every two weeks via subcutaneous injection in combination with a statin or other lipid-lowering therapies. ACM in August 2017 agreed to the proposed addition of 300 mg 4 weekly dosing (using two 150 mg injections consecutively at two different injection sites).
Comparator	Ezetimibe 10 mg oral tablet once daily or placebo in combination with a statin or other lipid-lowering therapies
Outcomes	Reduction in LDL-c leading to reduction in cardiovascular events (e.g. cardiovascular death, myocardial infarction, angina) and improved quality of life
Clinical claim	Alirocumab is superior in terms of efficacy and similar in terms of safety compared with ezetimibe and placebo

Source: Table 1.1.1, p2 of the submission  
Abbreviations: LDL-c, low density lipoprotein

### 2 Requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Published (Effective) Dispensed price for maximum quantity	Proprietary name and manufacturer
Alirocumab 75 mg/mL injection, 2 x 1 mL pre-filled pen	1	2	5	\$ [REDACTED] (\$ [REDACTED])	Praluent® Sanofi
Alirocumab 150 mg/mL injection, 2 x 1 mL pre-filled pen	1	2	5	\$ [REDACTED] (\$ [REDACTED])	

Note: The proposed prices were estimates based on ex-manufacturer prices and dispensing fees as of 1 July 2016. There was a slight increase in dispensing fees from 1 July 2017 that would have minimal impact on the economic analysis and financial estimates.

Category / Program:	Section 85
PBS Indication:	Clinical atherosclerotic cardiovascular disease and heterozygous familial hypercholesterolaemia

Treatment phase:	Initial/Continuation
Restriction:	Authority required
Treatment criteria/ Prescriber instructions:	<p>Treatment with alirocumab should be initiated by a consultant physician or in consultation with a consultant physician.</p> <p>All patients who initiate treatment with alirocumab should begin on the 75 mg dose once every 2 weeks. Patients should be followed up by the treating clinician after 4 weeks to determine whether dose up-titration to 150 mg once every 2 weeks is necessary.</p> <p>The date of the consultation with a consultant physician must be no more than 6 months prior to the application for a PBS authority. The full name of the consultant physician consulted and the date of consultation are to be provided at the time of application.</p> <p>The qualifying LDL-c cholesterol level must be provided at the time of application and must be within 2 months of the consultation date. With the exception of patients contraindicated to a statin, the agent, dose and duration of statin treatment must be provided at the time of application.</p>
Clinical criteria:	<p>The treatment must be in conjunction with dietary therapy and exercise</p> <p>AND</p> <p>Patient must have heterozygous familial hypercholesterolaemia, confirmed by: Genetic testing, OR</p> <p>A Dutch Lipid Clinic Network Score of at least 6</p> <p>AND</p> <p>Patient must have coronary heart disease, OR Patient must have symptomatic cerebrovascular disease, OR Patient must have peripheral vascular disease</p> <p>AND</p> <p>Patient must have an LDL-c cholesterol level in excess of 2.6 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 2.6 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 2.6 millimoles per litre and must be one in whom treatment with an HMG CoA reductase inhibitor (statin) is contraindicated.</p>
Population criteria:	Adults aged ≥ 18 years with clinical atherosclerotic cardiovascular disease and heterozygous familial hypercholesterolaemia

- 2.1 The requested restriction narrows the eligible population to a subset of patients with higher overall cardiovascular risk (i.e. HeFH AND pre-existing ASCVD) compared with the TGA approved indication which covers a broader hypercholesterolaemia population (i.e. HeFH OR non-familial clinical ASCVD).
- 2.2 The LDL-c threshold included in the proposed restriction was poorly justified and was not consistent with the available clinical evidence, treatment guidelines or current restrictions for ezetimibe. The ESC considered the proposed clinical criteria for the PBS listing, especially LDL-c levels and Dutch Lipid Clinic Network Score (DLCNS) >6, may not adequately identify HeFH. The Pre-Sub-Committee Response (PSCR) (p1)

stated the LDL-c cut off of 2.6 mmol/L was chosen for consistency with the minimum of mean baseline LDL-c observed across the alirocumab clinical trials and that a threshold of 2.6 mmol/L would enable patients treated with alirocumab to reach target levels defined in Australian clinical practice guidelines (1.8 mmol/L). The ESC 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 alirocumab. The PBAC noted that a DLCNS of between 6-8 indicated probable familial hypercholesterolaemia. The PBAC also noted from the pre-PBAC response (p1) that while a threshold LDL-c of 2.6 mmol/L may be consistent with the minimum mean doses across the alirocumab trials, mean baseline LDL-C was higher in the FH trials: FH I (3.8 mmol/L; SD: 1.3), FH II (3.4 mmol/L; SD: 1.1), HIGH FH (5.1 mmol/L; SD: 1.5).

- 2.3 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 ‘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.
- 2.4 The submission proposed the same price for the 75 mg and 150 mg dose strengths, both subject to special pricing arrangements with a [REDACTED] % rebate on the published DPMQ or a [REDACTED] % rebate on the published ex-manufacturer price.

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

### **3 Background**

#### **Registration status**

- 3.1 Alirocumab was approved by the TGA on 17 May 2016 for the following indication:
- As an adjunct to diet and exercise, in adults with heterozygous familial hypercholesterolaemia or clinical atherosclerotic cardiovascular disease:
- In combination with a statin, or statin with other lipid-lowering therapies or,
  - In combination with other lipid-lowering therapies in patients who are statin-intolerant.

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

3.2 A subsequent request for extension of indication and changes to dosage was accepted for evaluation by the TGA on 31 August 2016. Proposed changes to the indication based on the TGA delegate's overview include broadening the patient population to include patients with non-familial hypercholesterolaemia or mixed dyslipidaemia; and dosage changes to allow 300 mg every 4 weeks as starting and maintenance doses. The TGA delegate's decision from 3 July 2017 indicated no extension to the indication as proposed, but allowed for the change in dosage. The ACM minutes from the 4 August 2017 meeting indicated:

- the ACM noted there was not sufficient data to support the inclusion of all patients with non-familial hypercholesterolaemia.
- the ACM agreed that if the patient group was at very high/high risk only for cardiovascular event and mixed dyslipidaemia then the efficacy and safety data provided for this submission of alirocumab was supportive of the treatment for that patient group.
- the ACM agreed that the increased C<sub>max</sub> and smaller increase in exposure seen with the proposed 300 mg Q4W dosing, and increase in concentration is acceptable.

## **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 submission is patients with HeFH who also have ASCVD and high LDL-c levels (>2.6mmol/L). These patients are described as being at high risk of experiencing subsequent cardiovascular events.

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

## **5 Comparator**

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

5.2 The submission did not consider evolocumab as a comparator as it is currently PBS-listed for homozygous familial hypercholesterolaemia patients only. The PBAC considered evolocumab should be considered a relevant near market comparator given its similarity to alirocumab (same drug class) with overlapping indications. Evolocumab was also considered by the PBAC at the November 2017 meeting for a broader indication (familial hypercholesterolaemia and hypercholesterolaemia with symptomatic atherosclerotic cardiovascular disease who do not have underlying familial hypercholesterolaemia) that will overlap the proposed target population for alirocumab.

- 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, 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 alirocumab.

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

## **6 Consideration of the evidence**

### **Sponsor hearing**

- 6.1 There was no hearing for this item.

### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from individuals (13), health care professionals (4) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described the benefits of treatment with alirocumab including the strong conviction that PCSK9 inhibitors will be able to prevent or reverse ASCVD and save lives of patients with familial hypercholesterolaemia.

### **Clinical trials**

- 6.3 The submission was based on a meta-analysis of 7 head-to-head randomised trials comparing alirocumab with placebo (ODYSSEY FH I, ODYSSEY FH II, ODYSSEY HIGH FH, ODYSSEY COMBO I, ODYSSEY LONG TERM, ODYSSEY JAPAN and Stein 2012) and a meta-analysis of 4 head-to-head randomised trials comparing alirocumab with ezetimibe (ODYSSEY COMBO II, ODYSSEY ALTERNATIVE, ODYSSEY OPTIONS I, ODYSSEY OPTIONS II).
- 6.4 The submission excluded several trials that may have been informative that were included for further consideration during the evaluation: ODYSSEY CHOICE I, ODYSSEY CHOICE II, ODYSSEY ESCAPE, EFC14074, McKenney 2012 and Roth 2012.
- 6.5 The ODYSSEY OUTCOMES trial is a large (n=18,600), ongoing trial evaluating cardiovascular outcomes (e.g. CHD death, non-fatal MI, fatal and non-fatal ischaemic stroke and unstable angina requiring hospitalisation) in patients with hypercholesterolaemia who have recently experienced an acute coronary syndrome who are receiving alirocumab 75 mg/150 mg versus placebo on background statin therapy. The follow-up period is approximately 5 years and results are expected in early 2018.
- 6.6 Details of the included trials are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
<b>Placebo-controlled trials</b>		
ODYSSEY FH I (EFC12492)	Sanofi Clinical Study Report (2014). A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of alirocumab in Patients With Heterozygous Familial Hypercholesterolemia Not Adequately Controlled With Their Lipid-Modifying Therapy.	Internal study report
	Kastelein JJP, Ginsberg HN, Langslet G 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, 13(43):2996-3003
	Kastelein JJP, Robinson JG, Farnier M et al (2014). Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia not adequately controlled with current lipid-lowering therapy: Design and rationale of the ODYSSEY FH studies.	Cardiovascular Drugs and Therapy, 28(3):281-289
ODYSSEY FH II (CL1112)	Sanofi Clinical Study Report (2014). A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy.	Internal study report
	Kastelein JJP, Ginsberg HN, Langslet G 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, 13(43):2996-3003
	Kastelein JJP, Robinson JG, Farnier M et al (2014). Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia not adequately controlled with current lipid-lowering therapy: Design and rationale of the ODYSSEY FH studies.	Cardiovascular Drugs and Therapy, 28(3):281-289
ODYSSEY HIGH FH (EFC12732)	Sanofi Clinical Study Report (2014). A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of alirocumab in Patients With Heterozygous Familial Hypercholesterolemia and LDL-c higher or equal to 160 mg/dL With Their Lipid-Modifying Therapy.	Internal study report
	Ginsberg HN, Rader DJ, Raal FJ et al (2016). Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia and LDL-c of 160 mg/dl or Higher.	Cardiovascular Drugs and Therapy, 30:473–483
	Kastelein JJP, Robinson JG, Farnier M et al (2014). Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia not adequately controlled with current lipid-lowering therapy: Design and rationale of the ODYSSEY FH studies.	Cardiovascular Drugs and Therapy, 28(3):281-289
ODYSSEY CHOICE I	Regeneron Clinical Study Report (2016). A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of an Every Four Weeks Treatment Regimen of Alirocumab in Patients with Primary Hypercholesterolaemia.	Internal study report
	Roth EM, Moriarty PM, Bergeron J 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	Sanofi Clinical Study Report (2015). A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Evaluating the Efficacy and Safety of Alirocumab in Patients with Primary Hypercholesterolemia not treated with a statin.	Internal study report
	Stroes E, Guyton JR, Lepor N et al (2016). ODYSSEY CHOICE II Investigators. Efficacy and Safety of Alirocumab 150 mg Every 4 Weeks in Patients With Hypercholesterolemia Not on Statin Therapy: The ODYSSEY CHOICE II Study.	Journal of the American Heart Association, doi: 10.1161/JAHA.116.003421.
ODYSSEY COMBO I	Sanofi Clinical Study Report (2014). A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of alirocumab in High Cardiovascular Risk Patients With Hypercholesterolemia	Internal study report

Trial ID	Protocol title/ Publication title	Publication citation
(EFC11568)	Not Adequately Controlled With Their Lipid-Modifying Therapy.	
	Kereiakes DJ, Robinson JG, Cannon CP 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
	Colhoun HM, Robinson JG, Farnier M et al (2014). Efficacy and safety of alirocumab, a fully human PCSK9 monoclonal antibody, in high cardiovascular risk patients with poorly controlled hypercholesterolemia on maximally tolerated doses of statins: rationale and design of the ODYSSEY COMBO I and II trials.	BMC Cardiovascular Disorders, 14:121
ODYSSEY LONG TERM (LTS11717)	Sanofi Clinical Study Report (2014). A Randomized, Double-Blind, Placebo-Controlled, Long-term safety and tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with their Lipid Modifying Therapy.	Internal study report
	Robinson JG, Farnier M, Krempf M et al (2015). Efficacy and safety of alirocumab in reducing lipids and cardiovascular events.	New England Journal of Medicine 372: 1489–1499
ODYSSEY JAPAN (EFC13672)	Sanofi Clinical Study Report (2016). A randomized, double-blind, placebo-controlled, parallel group, multicenter study to evaluate the efficacy and safety of alirocumab in heterozygous familial hypercholesterolemia or high cardiovascular risk patients with hypercholesterolemia not adequately controlled with their lipid modifying therapy.	Internal study report
	Teramoto T et al (2016). Efficacy and safety of alirocumab in Japanese patients with hypercholesterolemia on stable statin therapy: First data with the 75 mg every two weeks dose.	Circulation Journal, 80:1980-87
McKenney 2012	Sanofi Clinical Study Report (2012). A randomized, double-blind, parallel-group, placebo-controlled, multicenter study evaluating the efficacy and safety of five doses and two dose regimens of SAR236553 over 12 weeks in patients with primary hypercholesterolemia and LDL-cholesterol $\geq 100$ mg/dL ( $\geq 2.59$ mmol/L) on ongoing stable atorvastatin therapy.	Internal study report
	McKenney JM, Koren MJ, Kereiakes DJ 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(25):2344-2353
Stein 2012 (CL1003)	Regeneron Clinical Study Report (2012). A Randomized, Double-Blind, Placebo-Controlled, 12-Week Study of the Safety and Efficacy of REGN727 in Patients with Heterozygous Familial Hypercholesterolemia.	Internal study report
	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
EFC14074	Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab (SAR236553/REGN727) in High Cardiovascular Risk Patients With Hypercholesterolemia Not Adequately Controlled With Their Lipid Modifying Therapy in South Korea and Taiwan.	ClinicalTrials.gov, NCT02289963
ODYSSEY ESCAPE	Study of Alirocumab (REGN727/SAR236553) in Patients With Heterozygous Familial Hypercholesterolemia (HeFH) Undergoing Low-density Lipoprotein (LDL-c) Apheresis Therapy (ESCAPE).	ClinicalTrials.gov, NCT02326220
Roth 2012	A randomized, double-blind, parallel-group, placebo-controlled, fixed dose/dose regimen, multicenter study evaluating the efficacy and safety of SAR236553 when co-administered with 80 mg of atorvastatin over 8 weeks in patients with primary hypercholesterolemia and LDL-cholesterol $\geq 100$ mg/dL ( $\geq 2.59$ mmol/L) on atorvastatin 10 mg.	Internal study report
	Roth EM, McKenney JM, Hanotin C et al (2012). Atorvastatin with or without	New England Journal of

Trial ID	Protocol title/ Publication title	Publication citation
	an antibody to PCSK9 in primary hypercholesterolemia.	Medicine, 367(20):1891-900
Stein 2012	A Randomized, Double-Blind, Placebo-Controlled, 12-Week Study of the Safety and Efficacy of REGN727 in Patients with Heterozygous Familial Hypercholesterolemia.	Internal study report
	Stein EA, Gipe D, Bergeron J 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.
<b>Ezetimibe-controlled trials</b>		
ODYSSEY COMBO II (EFC11569)	Sanofi Clinical Study Report (2014). A Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab Versus Ezetimibe in High Cardiovascular Risk Patients With Hypercholesterolemia Not Adequately Controlled With Their Statin Therapy.	Internal study report
	Cannon CP, Cariou B, Blom D 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
	Colhoun HM, Robinson JG, Farnier M et al (2014). Efficacy and safety of alirocumab, a fully human PCSK9 monoclonal antibody, in high cardiovascular risk patients with poorly controlled hypercholesterolemia on maximally tolerated doses of statins: rationale and design of the ODYSSEY COMBO I and II trials.	BMC Cardiovascular Disorders, 14:121
ODYSSEY ALTERNATIVE NCT01709513	Regeneron Clinical Study Report (2014). A Randomized, Double-Blind, Double-Dummy, Active-Controlled Study to Evaluate the Efficacy and Safety of Alirocumab in Patients with Primary Hypercholesterolemia Who Are Intolerant to Statins.	Internal study report
	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
	Moriarty PM, Jacobson TA, Bruckert E et al (2014). Efficacy and safety of alirocumab, a monoclonal antibody to PCSK9, in statin-intolerant patients: design and rationale of ODYSSEY ALTERNATIVE, a randomized phase 3 trial.	Journal of Clinical Lipidology, 8(6):554-561
ODYSSEY OPTIONS I (CL1110)	Regeneron Clinical Study Report (2014). A Randomized, Double-Blind Study of the Efficacy and Safety of Alirocumab Added on to Atorvastatin Versus Ezetimibe Added on to Atorvastatin Versus Atorvastatin Dose Increase Versus Switch to Rosuvastatin in Patients Who Are Not Controlled on Atorvastatin.	Internal study report
	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(8):3140-8
	Robinson JG, Colhoun HM, Bays HE et al (2014). Efficacy and safety of alirocumab as add-on therapy in high-cardiovascular-risk patients with hypercholesterolemia not adequately controlled with atorvastatin (20 or 40 mg) or rosuvastatin (10 or 20mg): Design and rationale of the odyssey options studies.	Clinical Cardiology, 37(10):597-604
ODYSSEY OPTIONS II (CL1118)	Regeneron Clinical Study Report (2014). A Randomized, Double-Blind Study of the Efficacy and Safety of Alirocumab Added-on to Rosuvastatin versus Ezetimibe Added-on to Rosuvastatin versus Rosuvastatin Dose Increase in patients Who are Not Controlled on Rosuvastatin.	Internal study report
	Farnier M, Jones P, Severance R et al (2016). Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the	Atherosclerosis, 244:138-46

Trial ID	Protocol title/ Publication title	Publication citation
	rosuvastatin dose in high cardiovascular risk patients: The ODYSSEY OPTIONS II randomized trial.	
	Robinson JG, Colhoun HM, Bays HE et al (2014). Efficacy and safety of alirocumab as add-on therapy in high-cardiovascular-risk patients with hypercholesterolemia not adequately controlled with atorvastatin (20 or 40 mg) or rosuvastatin (10 or 20mg): Design and rationale of the odyssey options studies.	Clinical Cardiology, 37(10):597-604

Source: Table 2.2.1, pp47-48 of the submission, clinical trial reports and publications

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

**Table 3: Key features of the included evidence**

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Alirocumab versus placebo</b>						
ODYSSEY FH I	486	MC, R, DB, PG 78 weeks	Low	HeFH	Change in LDL-c levels	Not used
ODYSSEY FH II	249	MC, R, DB, PG 78 weeks	Low	HeFH	Change in LDL-c levels	Not used
ODYSSEY HIGH FH	107	MC, R, DB, PG 78 weeks	Unclear	HeFH with high LDL-c levels	Change in LDL-c levels	Not used
ODYSSEY COMBO I	316	MC, R, DB, PG 52 weeks	Low	High risk non-familial	Change in LDL-c levels	Not used
ODYSSEY LONG TERM	2341	MC, R, DB, PG 78 weeks	Low	HeFH or high risk non-familial	Change in LDL-c levels	Not used
ODYSSEY JAPAN	216	MC, R, DB, PG 52 weeks	Low	HeFH or high risk non-familial	Change in LDL-c levels	Not used
Stein 2012 <sup>a</sup>	77	MC, R, DB 5 treatment arms 12 weeks	Low	HeFH	Change in LDL-c levels	Not used
ODYSSEY CHOICE I	803	MC, R, DB, PG 4 treatment arms 48 weeks	Low	Concomitant statin or not treated with statin <sup>b</sup>	Change in LDL-c levels	Not used
ODYSSEY CHOICE II	233	MC, R, DB, PG 4 treatment arms 48 weeks	Unclear	Not treated with statin <sup>b</sup>	Change in LDL-c levels	Not used
ODYSSEY ESCAPE	62	MC, R, DB, PG 18 weeks	Low	HeFH undergoing LDL-c apheresis	Rate of apheresis treatments	Not used
EFC14074	199	MC, R, DB, PG 52 weeks	Low	High risk non-familial	Change in LDL-c levels	Not used
McKenney 2012 <sup>a</sup>	183	MC, R 6 treatment arms 12 weeks	Low	Concomitant fixed dose statin only <sup>b</sup>	Change in LDL-c levels	Not used
Roth 2012 <sup>a</sup>	92	MC, R, DB, AC, PG 3 treatment arms 8 weeks	Low	Concomitant fixed dose statin only <sup>b</sup>	Change in LDL-c levels	Not used

<b>Alirocumab versus ezetimibe</b>						
ODYSSEY COMBO II	720	MC, R, DB, PG 104 weeks	Low	High risk non-familial	Change in LDL-c levels	Not used
ODYSSEY ALTERNATIVE	314	MC, R, DB, AC, PG 3 treatment arms 24 weeks	Low	Statin intolerant <sup>a</sup>	Change in LDL-c levels	Not used
ODYSSEY OPTIONS I	355	MC, R, DB, PG 7 treatment arms 24 weeks	Low	Concomitant fixed dose statin <sup>b</sup>	Change in LDL-c levels	Not used
ODYSSEY OPTIONS II	305	MC, R, DB, PG 7 treatment arms 24 weeks	Low	Concomitant fixed dose statin <sup>b</sup>	Change in LDL-c levels	Not used

Source: Compiled during the evaluation using Table 2.4.1, pp67-74, Table 2.4.4, pp79 of the submission, clinical trial reports and publications

Abbreviations: AC, active control; DB, double blind; HeFH, heterozygous familial hypercholesterolaemia; LDL-c, low density lipoprotein cholesterol; MC, multi-centre; PG, parallel-group; R, randomised.

<sup>a</sup> Phase 2 trials

<sup>b</sup> Patients with primary hypercholesterolaemia (heterozygous familial or non-familial)

Note: The ODYSSEY CHOICE I, ODYSSEY CHOICE II, ODYSSEY ESCAPE, EFC14074, McKenney 2012 and Roth 2012 trials were included during the evaluation.

- 6.8 Three of the study sites in the ODYSSEY HIGH FH trial (with 20 randomised patients) were closed due to serious breaches of compliance with Good Clinical Practice. It was unclear if this could introduce potential biases given the relatively small trial population of 107 patients in total with 35 patients in the placebo arm.
- 6.9 There was a randomisation error reported in the ODYSSEY CHOICE II trial resulting in fewer patients in one of the intervention arms than planned. However, the investigators determined that the trial had sufficient statistical power for efficacy. It was unclear if the systematic allocation error may have introduced other potential biases.
- 6.10 The included trials appear to have limited applicability to the requested PBS population in terms of baseline cardiovascular risk.
- 6.11 The main outcome of change in LDL-c levels from baseline in the trials was not used in the economic evaluation. The submission instead used change in TC:HDL cholesterol ratio based on post-hoc analyses from two trials (ODYSSEY COMBO II and ALTERNATIVE), transformed to cardiovascular outcomes in the economic model.

### **Comparative effectiveness**

- 6.12 The main outcome of the submission was mean change in LDL-c levels from baseline with alirocumab, ezetimibe and placebo.

**Table 4: Mean percentage change in calculated LDL-c levels in mixed hypercholesterolaemia populations**

Trial	Alirocumab, Mean, % (SE)	Ezetimibe, Mean, % (SE)	Placebo, Mean,% (SE)	Treatment difference, Mean, % (95% CI)
<b>75/150 mg fortnightly, Baseline to Week 24</b>				
ODYSSEY FH I (HeFH)	-48.8 (1.6)	-	9.1 (2.2)	<b>-57.9 (-63.3, -52.6)</b>
ODYSSEY FH II (HeFH)	-48.7 (1.9)	-	2.8 (2.8)	<b>-51.4 (-58.1, -44.8)</b>
ODYSSEY COMBO I (High risk non-FH)	-48.2 (1.9)	-	-2.3 (2.7)	<b>-45.9 (-52.5, -39.3)</b>
ODYSSEY JAPAN (HeFH or high risk non-FH)	-62.5 (1.3)	-	1.6 (1.8)	<b>-64.1 (-68.5, -59.8)</b>
ODYSSEY CHOICE I (no statin)	-50.2 (3.7)	-	-0.3 (2.7)	<b>-49.8 (-60.2, -39.4)</b>
ODYSSEY CHOICE I (concomitant statin)	-51.6 (3.3)	-	-0.1 (2.3)	<b>-51.5 (-60.4, -42.6)</b>
ODYSSEY CHOICE II (statin intolerant)	-53.5 (1.6)	-	4.7 (2.3)	<b>-58.2 (-63.8, -52.7)</b>
EFC14074 (High risk non-FH)	-57.1 (3.0)	-	6.3 (2.9)	<b>-63.4 (-71.6, -55.2)</b>
ODYSSEY COMBO II (High risk non-FH)	-50.6 (1.4)	-20.7 (1.9)	-	<b>-29.8 (-34.4, -25.3)</b>
ODYSSEY ALTERNATIVE (statin intolerant)	-45.0 (2.2)	-14.6 (2.2)	-	<b>-30.4 (-36.6, -24.2)</b>
ODYSSEY OPTIONS I (atorvastatin 20 mg)	-44.1 (4.5)	-20.5 (4.7)	-	<b>-23.6 (-40.7, -6.5)<sup>a</sup></b>
ODYSSEY OPTIONS I (atorvastatin 40 mg)	-54.0 (4.3)	-22.6 (4.3)	-	<b>-31.4 (-47.4, -15.4)<sup>a</sup></b>
ODYSSEY OPTIONS II (rosuvastatin 10 mg)	-50.6 (4.2)	-14.4 (4.4)	-	<b>-36.1 (-51.5, -20.7)<sup>b</sup></b>
ODYSSEY OPTIONS II (rosuvastatin 20 mg)	-36.3 (7.1)	-11.0 (7.2)	-	-25.3 (-50.9, 0.3) <sup>b</sup>
<b>150 mg fortnightly fixed dose, Baseline to Week 6/8/12/24</b>				
ODYSSEY HIGH FH (HeFH)	-45.7 (3.5)	-	-6.6 (4.9)	<b>-39.1 (-51.1, -27.1)</b>
ODYSSEY LONG TERM (HeFH or high risk non-FH)	-61.0 (0.7)	-	0.8 (1.0)	<b>-61.9 (-64.3, -59.4)</b>
Stein 2012 (HeFH)	-67.9 (4.9)	-	-10.7 (5.0)	<b>-57.3 (-70.9, -43.6)</b>
ODYSSEY ESCAPE (lipid apheresis)	-53.6 (2.3)	-	1.6 (3.1)	<b>-55.3 (-63.1, -47.5)</b>
McKenney 2012 (concomitant statin only)	-72.4 (3.2)	-	-5.1 (3.1)	<b>-67.3 (-76.1, -58.5)</b>
Roth 2012 (atorvastatin 10 mg)	-66.2 (3.5)	-	-17.3 (3.5) <sup>c</sup>	<b>-48.8 (-58.6, -39.0)</b>
Roth 2012 (atorvastatin 80 mg)	-73.2 (3.5)	-	-17.3 (3.5) <sup>c</sup>	<b>-55.8 (-65.6, -46.0)</b>

Trial	Alirocumab, Mean, % (SE)	Ezetimibe, Mean, % (SE)	Placebo, Mean,% (SE)	Treatment difference, Mean, % (95% CI)
<b>150 mg 4 weekly/150 mg fortnightly, Baseline to Week 24</b>				
ODYSSEY CHOICE II (statin intolerant)	-51.7 (2.3)	-	4.7 (2.3)	<b>-56.4 (-62.9, -49.9)</b>
<b>300 mg 4 weekly/150 mg fortnightly, Baseline to Week 24</b>				
ODYSSEY CHOICE I (no statin)	-52.7 (1.9)	-	-0.3 (2.7)	<b>-52.4 (-59.8, -45.0)</b>
ODYSSEY CHOICE I (concomitant statin)	-58.8 (1.6)	-	-0.1 (2.3)	<b>-58.7 (-65.0, -52.4)</b>
<b>150 mg 4 weekly fixed dose, Baseline to Week 12</b>				
Stein 2012 (HeFH)	-28.9 (5.1)	-	-10.7 (5.0)	<b>-18.2 (-32.2, -4.3)</b>
<b>300 mg 4 weekly fixed dose, Baseline to Week 12</b>				
McKenney 2012 (concomitant statin only)	-47.7 (3.2)	-	-5.1 (3.1)	<b>-42.6 (-51.4, -33.9)</b>
Stein 2012 (HeFH)	-42.5 (5.1)	-	-10.7 (5.0)	<b>-31.9 (-45.8, -18.0)</b>

Source: Table 2.5.1 (p94), Table 2.5.2 (p96) of the submission; Table 29 (p152), Table 31 (p154), of the ODYSSEY CHOICE I trial report; Table 22 (p113), Table 23 (p114), of the ODYSSEY CHOICE II trial report; Table 19 (p86), of the EFC14074 trial report; p3592 of Moriarty 2016 – ODYSSEY ESCAPE trial publication; Table 17 (p88), of the McKenney 2012 trial report; Table 17 (pp72-73), of the Roth 2012 trial report; Table 12 (p80) of the Stein 2012 trial report

Abbreviations: CI, confidence interval; LDL-c, low-density lipoprotein

<sup>a</sup> 99% confidence interval

<sup>b</sup> 98.75% confidence interval

Results in bold were statistically significant

Note: The ODYSSEY CHOICE I, ODYSSEY CHOICE II, ODYSSEY ESCAPE, EFC14074, McKenney 2012, Roth 2012 and Stein 2012 (alirocumab 150 mg and 300 mg 4 weekly arms) trials were included during the evaluation.

- 6.13 Treatment with alirocumab 75 mg (up-titratable to 150 mg) fortnightly was associated with statistically significant decreases in LDL-c levels compared to placebo (approximately 50-60% reduction) in all patient groups.
- 6.14 Treatment with alirocumab 150 mg fortnightly (fixed dose) was associated with statistically significant decreases in LDL-c levels compared to placebo (approximately 50-60%).
- 6.15 Patients receiving other doses of alirocumab (150 mg or 300 mg 4-weekly, up-titratable to 150 mg fortnightly) had statistically significant LDL-c reductions compared to placebo (approximately 50-60%). Treatment with alirocumab 150 mg and 300 mg 4-weekly fixed doses was associated with a statistically significant LDL-c reduction (approximately 20% and 30-40% respectively) compared with placebo which were numerically lower than observed with other alirocumab dose regimens.
- 6.16 Although the treatment effect of alirocumab was broadly consistent in terms of decreases in LDL-c levels from baseline across dose strengths, the treatment difference observed when comparing alirocumab with placebo appeared to vary (with notably lower estimates in the ODYSSEY COMBO I and HIGH FH trials). This may be due to differences in background therapy between arms within the trials.
- 6.17 When compared to ezetimibe, treatment with alirocumab 75 mg (up-titratable to 150 mg) was associated with statistically significant decreases in LDL-c levels (approximately 20-30% reduction).

- 6.18 The submission presented meta-analyses comparing alirocumab with placebo or ezetimibe based on combinations of trials administering alirocumab 75/150 mg fortnightly or 150 mg fortnightly fixed dose. The results showed statistically significant decreases in LDL-c levels when comparing alirocumab with placebo or ezetimibe, similar to individual trial results. However, results from the meta-analyses may not be reliable due to substantial heterogeneity between the trials (differences in patient populations of familial versus non-familial disease, baseline LDL-c levels, degree of cardiovascular risk, background lipid therapy, alirocumab dosing regimens and titration schedules).
- 6.19 Results from subgroup analyses indicated that there were differences in LDL-c reduction observed suggesting a number of potential treatment effect modifiers (e.g. gender, ethnicity, region, baseline PCSK9 levels, diabetes and baseline HDL). However, there was no consistent effect modification evident.
- 6.20 Treatment effect differences were observed in subgroup analyses in patients receiving alirocumab who required up-titration compared with patients who remained on a lower dose. When compared with patients in the not up-titrated subgroups, patients who were up-titrated had numerically lower percentage reductions in LDL-c from baseline to week 12 (approximately 20% difference). The observed difference in treatment effect between subgroups based on up-titration was not further explored in the submission. There was insufficient information available in the trial reports to determine potential reasons for this observation.
- 6.21 The submission did not present data comparing the efficacy of various dose regimens of alirocumab. Included trials assessing different alirocumab dose regimens (ODYSSEY CHOICE I and II, Stein 2012 trials) were not designed (or statistically powered) for comparisons between alirocumab treatment arms.
- 6.22 Longer term studies suggest that short-term improvements in LDL-c levels may be maintained beyond 2 years while patients continue to be treated with alirocumab.
- 6.23 The submission presented responder analyses based on the proportion of patients achieving pre-specified LDL-c target thresholds with alirocumab, ezetimibe and placebo in the trials.
- 6.24 The majority of patients receiving alirocumab (all dose regimens except for 150 mg 4 weekly) achieved LDL-c levels of <2.59 mmol/L or <1.8 mmol/L (approximately 60-100%). Treatment with alirocumab 150 mg 4 weekly was associated with numerically lower proportions of patients achieving LDL-c levels of <2.59 mmol/L (27%) and <1.81 mmol/L (13%) compared to other dosing regimens.
- 6.25 The majority of patients in the ezetimibe arms of the trials achieved LDL-c targets of <2.59 mmol/L (approximately 70-80%) and approximately 40-50% of patients achieved an LDL-c <1.81 mmol/L. However, a lower proportion of statin-intolerant patients who were treated with ezetimibe with or without other non-statin therapy achieved LDL-c targets of <2.59 mmol/L (10%) and <1.81 mmol/L (1%).
- 6.26 There was a wide range of response measured in the placebo arms with approximately 3% to 60% of patients achieving target LDL-c levels of <2.59 mmol/L. The varying response observed in the placebo arms may be due to differences in

background therapy, baseline LDL-c levels and disease severity (familial, non-familial, cardiovascular risk) between trials.

- 6.27 The submission provided supportive analyses for cardiovascular outcomes based on safety data from the ODYSSEY LONG TERM trial, a published meta-analysis of 10 alirocumab trials (Ray et al. 2017), the ezetimibe IMPROVE-IT study (Cannon et al. 2015), the Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis of statin trials (Baigent et al. 2010) and the evolocumab cardiovascular outcomes trial, FOURIER (Sabatine et al. 2017).
- 6.28 The results from the evidence were inconsistent with some studies showing improvement in composite endpoints of major cardiovascular events and others showing no apparent differences. There was no apparent difference in angina, coronary death, cardiovascular death or all-cause mortality between arms in both the CTTC meta-analysis and the IMPROVE-IT study. The most recent evidence based on the evolocumab cardiovascular outcomes trial, FOURIER (N=27,564) suggests that the treatment effect of LDL-c lowering due to evolocumab is associated with a decrease in risk of non-fatal events of myocardial infarction, ischaemic stroke and coronary revascularisation and no apparent differences in cardiovascular death or all-cause mortality between treatment arms. The PBAC noted the FOURIER trial was not powered to show a mortality benefit and considered that given the hard major adverse cardiac events (MACE) and extended MACE endpoints were unequivocally positive in the FOURIER trial data it is plausible that these differences would lead to better survival with longer than two years follow-up. The PBAC considered the results of the ODYSSEY OUTCOMES trial will provide more certainty about the extent of cardiovascular benefits with alirocumab.
- 6.29 The submission presented additional data to support the relationship between the surrogate (LDL-c reductions) and final outcomes (cardiovascular events). Overall, the current evidence supports the hypothesis that a reduction in LDL-c levels is associated with a reduction in cardiovascular risk. The effect on mortality is less well defined as the recent trials (FOURIER, IMPROVE-IT) were not powered to detect a mortality benefit and may require longer term follow-up.
- 6.30 A comparison of percentage change in lipid levels for the ODYSSEY COMBO II and ALTERNATIVE trials is presented in Table 5 below.

Table 5: Comparison of percentage change in LDL-c and TC:HDL ratio (post-hoc analyses) from baseline

Endpoint	Percent change in TC:HDL from baseline to endpoint			Percent change in LDL-c from baseline to endpoint		
	Alirocumab 75/150 mg, Mean (SE)	Ezetimibe 10 mg, Mean (SE)	Treatment difference, Mean (95% CI)	Alirocumab 75/150 mg, Mean (SE)	Ezetimibe 10 mg, Mean (SE)	Treatment difference, Mean (95% CI)
<b>ODYSSEY COMBO II (high risk non-familial), ITT analysis</b>						
Week 24	-33.2 (1.0)	-13.2 (1.4)	-20.0 (-23.3, -16.7)	-50.6 (1.4)	-20.7 (1.9)	-29.8 (-34.4, -25.3)
Week 52	-32.2 (1.0)	-11.9 (1.5)	-20.3 (-23.9, -16.8)	-49.5 (1.5)	-18.3 (2.1)	-31.2 (-36.3, -26.1)
<b>ODYSSEY COMBO II (high risk non-familial), On-treatment analysis</b>						
Week 24	-34.6 (0.9)	-14.2 (1.3)	-20.4 (-23.5, -17.3)	-52.4 (1.3)	-21.8 (1.8)	-30.6 (-34.9, -26.2)
Week 52	-34.0 (1.0)	-12.7 (1.4)	-21.3 (-24.7, -17.9)	-51.8 (1.5)	-19.7 (2.1)	-32.2 (-37.2, -27.1)
<b>ODYSSEY ALTERNATIVE (statin intolerant), ITT analysis</b>						
Week 24	-34.3 (1.7)	-14.8 (1.8)	-19.5 (-24.4, -14.7)	-45.0 (2.2)	-14.6 (2.2)	-30.4 (-36.6, -24.2)
<b>ODYSSEY ALTERNATIVE (statin intolerant), On-treatment analysis</b>						
Week 24	-41.0 (1.4)	-17.5 (1.4)	-23.5 (-27.4, -19.6)	-52.2 (2.0)	-17.1 (2.0)	-35.1 (-40.7, -29.5)

Source: Constructed during the evaluation based on Table 1-4 (pp4-11) of Attachment 14a Post hoc analyses; Table 2.5.2 (p96) of the submission; Table 27 (p122), p124, Table 33 (p125) of the ODYSSEY COMBO II trial report; Table 29 (p148) of the ODYSSEY ALTERNATIVE trial report

Abbreviations: CI, confidence interval; ITT, intention to treat; LDL-c, low density lipoprotein; SE, standard error; TC:HDL, total:high density lipoprotein cholesterol ratio

Estimates used in the economic model are in italics

- 6.31 The relationship between relative reductions in TC:HDL ratio and LDL-c levels did not appear consistent when comparing treatment effect differences between trials for the primary endpoint at week 24 (e.g. larger change in LDL-c versus smaller change in TC:HDL ratio, -29.8% versus -20.0% in ODYSSEY COMBO II; and smaller change in LDL-c versus larger change in TC:HDL ratio, -19.5% versus 30.4% in ODYSSEY ALTERNATIVE).
- 6.32 The results were similarly unpredictable when comparing relative reductions in LDL-c versus TC:HDL ratio respectively within each trial arm as observed in ODYSSEY COMBO II (alirocumab: -50.6% versus -33.2%, ezetimibe: -20.7% versus -13.2%) and ODYSSEY ALTERNATIVE trials (alirocumab: -34.3% versus -45.0%, ezetimibe: -14.8% versus -14.6%). This was not unexpected given that TC:HDL is a ratio that is dependent on a number of lipid parameters (i.e. LDL-c, HDL, VLDL-c) and the associated increase/decrease in each parameter.
- 6.33 The submission did not adequately justify the choice of results from different time points and use of the on-treatment analysis versus ITT population analysis. The results from the on-treatment analysis for the ODYSSEY ALTERNATIVE trial were more favourable compared to the ITT analysis (-23.5% versus -19.5% reduction in TC:HDL ratio) which may be subject to bias due to the relatively high discontinuation rates in the trial.
- 6.34 The submission did not reasonably justify the use of results based on relative reductions in TC:HDL ratio, transformed to cardiovascular outcomes in the economic model given the relationship between this surrogate outcome and cardiovascular risk appears uncertain. However, ESC noted that prior decisions by PBAC in lipid modifying therapy have historically accepted models using TC:HDL rather than LDL-c.

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

## Comparative harms

- 6.35 The incidence of adverse events was highly variable between trials and did not consistently favour alirocumab, ezetimibe or placebo. There were no apparent differences in the incidence of adverse events between various dose regimens of alirocumab.
- 6.36 The most frequently reported adverse events with alirocumab treatment were upper respiratory tract infections (nasopharyngitis, influenza), general disorders and administration site conditions (fatigue, injection site reactions), musculoskeletal (myalgia, muscle spasms, musculoskeletal pain) and gastrointestinal disorders (diarrhoea, nausea, constipation).
- 6.37 There were differences in treatment-related adverse event incidence observed between alirocumab and placebo treatment arms in the trials. The difference observed was primarily due to injection site reactions followed by gastrointestinal disorders (nausea, diarrhoea), musculoskeletal disorders (e.g. myalgia) and headache associated with alirocumab treatment.
- 6.38 There are limited safety data beyond 18 months available for alirocumab. Longer-term safety results are expected from the ODYSSEY OLE open-label extension study evaluating the long term safety and efficacy of alirocumab when added to lipid lowering therapy in patients with heterozygous familial hypercholesterolaemia with maximum follow-up of 176 weeks. No published results were available during the evaluation but trial completion was expected in June 2017.

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

## Benefits and harms

- 6.39 On the basis of direct evidence presented in the submission, the comparison of alirocumab 75 mg (up-titratable to 150 mg) fortnightly and ezetimibe in patients with heterozygous familial and non-familial hypercholesterolaemia resulted in:
- Approximately a 20-30% relative reduction in LDL-c levels over a 24-week treatment duration. This change is considered clinically meaningful.
  - No apparent difference in adverse events over a 24-week treatment duration.
- 6.40 On the basis of direct evidence presented in the submission, the comparison of alirocumab 75 mg (up-titratable to 150 mg) fortnightly and placebo in patients with heterozygous familial and non-familial hypercholesterolaemia resulted in:
- Approximately a 50-60% relative reduction in LDL-c levels over a 24-week treatment duration. This change is considered clinically meaningful.
  - No apparent difference in adverse events over a 24-week treatment duration.
- 6.41 On the basis of direct evidence presented in the submission, the comparison of alirocumab 150 mg fortnightly (fixed dose) and placebo in patients with heterozygous familial and non-familial hypercholesterolaemia resulted in:
- Approximately a 40-70% relative reduction in LDL-c levels over a 6-24 week treatment duration. This change is considered clinically meaningful.
  - No apparent difference in adverse events over a 6-24 week treatment duration.

- 6.42 On the basis of direct evidence presented in the submission, the comparison of alirocumab 150 mg 4 weekly (up-titratable to 150 mg) fortnightly and placebo in patients with heterozygous familial and non-familial hypercholesterolaemia with statin intolerance resulted in:
- Approximately a 56% relative reduction in LDL-c levels over a 24 week treatment duration. This change is considered clinically meaningful.
  - No apparent difference in adverse events over a 24 week treatment duration.
- 6.43 On the basis of direct evidence presented in the submission, the comparison of alirocumab 300 mg 4 weekly (up-titratable to 150 mg) fortnightly and placebo in patients with heterozygous familial and non-familial hypercholesterolaemia resulted in:
- Approximately a 50-60% relative reduction in LDL-c levels over a 24 week treatment duration. This change is considered clinically meaningful.
  - No apparent difference in adverse events over a 24 week treatment duration.
- 6.44 On the basis of direct evidence presented in the submission, the comparison of alirocumab 150 mg 4 weekly (fixed dose) and placebo in patients with heterozygous familial hypercholesterolaemia resulted in:
- Approximately an 18% relative reduction in LDL-c levels over a 12 week treatment duration. It is unclear whether this change is likely to be clinically meaningful.
  - No apparent difference in adverse events over a 12 week treatment duration.
- 6.45 On the basis of direct evidence presented in the submission, the comparison of alirocumab 300 mg 4 weekly (fixed dose) and placebo in patients with heterozygous familial and non-familial hypercholesterolaemia with statin intolerance resulted in:
- Approximately a 30-45% relative reduction in LDL-c levels over a 12 week treatment duration. This change is considered clinically meaningful.
  - No apparent difference in adverse events over a 12 week treatment duration.

### **Interpretation of clinical evidence**

- 6.46 The submission described alirocumab 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.
- 6.47 The submission described alirocumab as superior in terms of efficacy (based on surrogate outcome measures) and similar in terms of safety compared to placebo. The PBAC considered the efficacy claim is reasonable, however the safety claim was poorly supported given the difference in treatment-related adverse events reported in alirocumab treatment arms (primarily due to injection site reactions, gastrointestinal disorders, musculoskeletal disorders and headache) compared to placebo.
- 6.48 Relative treatment effects of LDL-c reduction associated with alirocumab were not always consistent across trial populations with subgroup analyses indicating a number of potential treatment effect modifiers (particularly by up-titration status). However, ESC noted no consistent treatment effect modifiers were seen.

- 6.49 The magnitude of cardiovascular benefit associated with incremental LDL-c reductions for alirocumab compared with existing therapies is unclear. Comparisons with ezetimibe and placebo were based on lipid outcomes. The PBAC considered the strength of association between LDL-c levels and cardiovascular outcomes is robust and consistent with the extensive body of knowledge of the benefits of LDL-c lowering, however, the ongoing outcomes trial ODYSSEY OUTCOMES, would provide more certainty about the extent of cardiovascular benefits with alirocumab in patients with FH and ASCVD.
- 6.50 There was limited availability of data comparing the efficacy of various dose strengths and regimens that can be administered with the dispensed quantities under the proposed restriction.
- 6.51 There was limited availability of cardiovascular outcome data and long-term safety data (>18 months) for alirocumab. However, ESC noted that no safety signals were noted in this population with evolocumab over longer-term studies. The PSCR (p2) stated there is consensus among leading Australian clinicians that there is no LDL-c threshold below which there is no further benefit, and no increased risk of adverse events related to the achievement of very low LDL-c levels (Kostner, Nicholls and Amerena, 2016).
- 6.52 The PBAC considered that the claim of superior comparative effectiveness versus both ezetimibe and placebo based on lipid outcomes was reasonable.
- 6.53 The PBAC considered that the claim of similar comparative safety was reasonable compared to ezetimibe, though not supported in comparison to placebo.

### **Economic analysis**

- 6.54 The submission presented a stepped economic evaluation of alirocumab 75 mg (up-titratable to 150 mg) fortnightly for the treatment of HeFH with ASCVD as an add-on therapy to statins, compared with ezetimibe (replacement to ezetimibe) or placebo in patients inadequately controlled on statins. A separate analysis was presented evaluating alirocumab as an add-on therapy to other non-statin therapies, compared with ezetimibe (replacement to ezetimibe) or placebo in statin intolerant patients.
- 6.55 No economic evaluation was presented for the use of alirocumab as add-on therapy to a statin and ezetimibe OR as add-on therapy to ezetimibe in statin-intolerant patients, although the ESC considered the results of the economic model when alirocumab is compared to placebo can be considered applicable in this clinical scenario.
- 6.56 No economic evaluation was presented for other fixed or up-titratable dose regimens (150 mg either fortnightly or 4 weekly or 300 mg 4 weekly) although there is potential for administration of these regimens under the proposed listing. However, ESC noted that the proposed flat pricing between the 75 mg and 150 mg means that this does not have financial implications.
- 6.57 Limited data from the clinical evidence were used in the economic model.
- 6.58 The economic evaluation was based on relative reductions in TC:HDL ratio from selected clinical trials and other modelled variables. The economic evaluation was presented as a cost-utility analysis (summarised in Table 6).

**Table 6: Key components of the economic evaluation**

Component	Description
Type of analysis	Cost-utility analysis
Outcomes	% reduction in TC:HDL, life years gained, quality-adjusted life years
Time horizon	35 years
Methods used to generate results	Markov cohort expected value analysis
Health states	Four health states: prior atherosclerotic cardiovascular disease, recurrent CHD (myocardial infarction or angina), CHD death and non-CHD death
Cycle length	Yearly
Transition probabilities	Transition probabilities were derived from the secondary prevention Framingham risk equation for a composite CHD event (D'Agostino 2000) using TC:HDL ratios adjusted for relative treatment effects. The probability of a composite CHD event was adjusted using a familial hypercholesterolaemia risk multiplier. The composite event probability was converted to individual probabilities of myocardial infarction, angina or CHD death using a time-varying distribution derived from the Framingham risk equations for primary CHD events (Anderson 1990) adjusted for secondary prevention. Probability of a non-CHD death was derived from ABS life tables adjusted for the proportion of deaths due to CHD.
Discount rate	5% for costs and outcomes
Software package	Excel 2010

Source: Table 3.1.1, p162 of the submission

Abbreviations: CHD, coronary heart disease; TC:HDL, total cholesterol to high density lipoprotein ratio

6.59 All patients start in the prior ASCVD health state (described as pre-incident CHD in the submission). In any year, patients can have no event or experience a CHD event (non-fatal myocardial infarction, angina or CHD death) or death unrelated to coronary heart disease (non-CHD death). Patients experiencing multiple non-fatal events accrue only the acute costs of each event. There were no ongoing chronic costs due to events. Once a patient has an event, the same chronic consequence is applied regardless of multiple events occurring. The model does not allow for treatment discontinuations, assuming all patients were 100% adherent to treatment with drug costs applied until they experienced a fatal event. The assumption of assumed 100% adherence is inconsistent with the trial data (76% - 90%) and was not accounted for in sensitivity analyses.

6.60 The ESC questioned the validity of the representative modelled populations given the small sample sizes that they are based upon, their baseline lipid levels and non-familial hypocholesterolaemia status.

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

Table 7: Key drivers of the model

Description	Method/Value	Impact
Treatment effect on coronary death	<p>The modelled approach using the Framingham risk equations resulted in a substantial reduction in mortality associated with alirocumab compared with ezetimibe and placebo. There are known issues with the Framingham risk equation regarding inappropriate extrapolation of estimates beyond the bounds of the risk equations (time horizon, patient age), localisation of equations (derived from US general population sample) to different settings, and lack of validation against other cardiovascular risk calculators.</p> <p>Recent trial evidence for evolocumab (PCSK9 inhibitor) and ezetimibe suggests no treatment effect on cardiovascular mortality. The ESC considered a long term reduction in CV death to be reasonable, however the magnitude and timing of this reduction should be reassessed.</p>	High, favours alirocumab
Transformation of TC:HDL outcomes to cardiovascular outcomes	<p>Relative change in TC:HDL ratio from post-hoc analyses of clinical trial data converted to absolute change using baseline values in synthesised populations. The selection of data was poorly justified given it was based on largely non-familial trial populations with limited applicability to the PBS population.</p> <p>Absolute TC:HDL levels and modelled population characteristics were converted to cardiovascular risk using the Framingham risk equation for secondary prevention (D'Agostino 2000) and distributed across CHD death, myocardial infarction and angina using the Framingham risk equation for primary prevention (Anderson 1991). The risk calculators were not applied to the data appropriately (use of individual risk calculators to predict population estimates, synthesis of short-term risk models to predict long-term risk). The ESC considered it inappropriate to assume the proportion of total fatal and non-fatal events are the same in a primary prevention (Anderson 1991) population as a secondary prevention (D'Agostino 2000) population.</p>	High, favours alirocumab
Familial hypercholesterolaemia risk multiplier	<p>An additional familial hypercholesterolaemia risk multiplier based on elevated risk compared to non-familial hypercholesterolaemia patients in secondary prevention was applied to the D'Agostino (2000) risk equation for CHD events. The clinical relevance of the source data was unclear given a number of limitations (retrospective observational study, lack of clinical diagnosis, use of LDL-c thresholds different to requested restriction).</p>	High, favours alirocumab

Description	Method/Value	Impact
Distribution of coronary events	The distribution of events derived from the Anderson (1991) Framingham risk equation for primary prevention was adjusted to account for increased risk in secondary prevention. The adjustment was based on the ratio of subsequent events to initial events reported in the D'Agostino (2000) patient sample. Estimates may not be reliable given the adjustment represent events occurring over different time periods.	High, favours alirocumab
Time horizon	<p>The economic model was based on a 35 year time horizon which appeared appropriate to capture the majority of costs and benefits in familial hypercholesterolaemia patients with atherosclerotic disease.</p> <p>The extrapolation to 35 years was based on Framingham risk equations designed to predict risk over shorter time periods (up to 4 years with D'Agostino, 2000; and up to 10 years with Anderson, 1991). A validation exercise conducted by the Framingham authors indicates that short-term risk models cannot be reliably combined to estimate long-term risks, particularly in high risk patients (Pencini 2009). The ESC considered it inappropriate to apply 10 year probabilities at each annual cycle to the CHD equation without adjusting for annual risk.</p>	High, favours alirocumab
Modelled patient population	<p>Characteristics of the modelled population with inadequate control on statins were synthesised from a high risk non-familial trial population (ODYSSEY COMBO II) and a post-hoc analysis of BEACH SAND survey patient profiles with LDL-c &gt; 2.6 mmol/L not treated with ezetimibe (n=17) that did not capture familial/non-familial status of patients.</p> <p>Characteristics of the modelled population with statin intolerance were based on patient and lipid characteristics from the statin-intolerant trial population (ODYSSEY ALTERNATIVE) and systolic blood pressure from the BEACH SAND survey subgroup (n=17).</p>	Moderate, favours alirocumab
Utility estimates for prior atherosclerotic disease health state (baseline state)	The utility estimate for patients with prior atherosclerotic disease was based on the average utility score for the general Australian population and a utility decrement associated with an acute myocardial infarction. The disutility associated with an acute MI was incorrectly applied to a chronic health state due to MI and angina events.	Moderate, favours alirocumab
Treatment adherence	Assumed perfect adherence	Unclear

Source: compiled during the evaluation

Abbreviations: CHD, coronary heart disease; LDL-c, low density lipoprotein; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9; TC:HDL, total cholesterol to high density lipoprotein ratio

6.62 The results of the modelled economic evaluation for the inadequate control on statin population (Table 8) and the statin intolerant population (Table 9) are summarised below.

Table 8: Stepped economic evaluation of alirocumab versus ezetimibe or placebo (inadequate control on statins)

Type of resource item	Alirocumab	Ezetimibe	Placebo	Incremental cost vs	
				Ezetimibe	Placebo
<b>Step 1: Trial-based TC:HDL outcomes used in cost-effectiveness analysis of incremental cost per % change in TC:HDL over a 52 week time horizon. Drug costs only</b>					
Costs	██████	██████	██████	██████	██████
% change in TC:HDL	-34.0%	-12.7%	0%	-21.3%	-34.0%
Incremental cost per 1% reduction in TC:HDL				██████	██████
<b>Step 2: Time horizon extrapolated to 5 years</b>					
Costs	██████	██████	██████	██████	██████
% change in TC:HDL	-34.0%	-12.7%	0%	-21.3%	-34.0%
Incremental cost per 1% reduction in TC:HDL				██████	██████
<b>Step 3: Transform outcomes to CHD events using trial-based patient and lipid characteristics, and Framingham risk equations. Include discount rate for drug costs. No discounting for outcomes</b>					
Costs	██████	██████	██████	██████	██████
CHD events	0.1400	0.1684	0.1840	-0.0284	-0.0440
Incremental cost per CHD event avoided				██████	██████
<b>Step 4: Transform outcomes to CHD events based on modelled patient population using trial-based patient characteristics, lipid characteristics from BEACH SAND survey subgroup and Framingham risk equations</b>					
Costs	██████	██████	██████	██████	██████
CHD events	0.1468	0.1765	0.1927	-0.0296	-0.0459
Incremental cost per CHD event avoided				██████	██████
<b>Step 5: Include familial hypercholesterolaemia risk multiplier</b>					
Costs	██████	██████	██████	██████	██████
CHD events	0.3466	0.4057	0.4637	-0.0591	-0.0901
Incremental cost per CHD event avoided				██████	██████
<b>Step 6: Include additional costs associated with management of CHD events. Include discount rate for CHD event costs. No discounting for outcomes</b>					
Costs	██████	██████	██████	██████	██████
CHD events	0.3466	0.4057	0.4637	-0.591	-0.091
Incremental cost per CHD event avoided				██████	██████
<b>Step 7: Transform outcomes to LYs. Include discount rate for outcomes</b>					
Costs	██████	██████	██████	██████	██████
LYs	3.9850	3.8566	3.7872	0.1284	0.1977
Incremental cost per LY gained				██████	██████
<b>Step 8: Transform LYs to QALYs using disutility for CHD events</b>					
Costs	██████	██████	██████	██████	██████
QALYs	3.2003	3.0962	3.0400	0.1041	0.1603
Incremental cost per QALY gained				██████	██████
<b>Step 9: Modelled time horizon extrapolated to 35 years</b>					
Costs	██████	██████	██████	██████	██████
QALYs	6.6181	5.9672	5.6540	0.6508	0.9641
Incremental cost per QALY gained				██████	██████

Source: Constructed during the evaluation based on data from the 'ALI\_model' Excel workbook  
 Abbreviations: CHD, coronary heart disease; HDL, high density lipoprotein; LYs, life years; TC, total cholesterol; QALYs, quality-adjusted

life years

**Table 9: Stepped economic evaluation of alirocumab versus ezetimibe or placebo (statin intolerant)**

Type of resource item	Alirocumab	Ezetimibe	Placebo	Incremental cost vs	
				Ezetimibe	Placebo
<b>Step 1: Trial-based TC:HDL outcomes used in cost-effectiveness analysis of incremental cost per % change in TC:HDL over a 52 week time horizon. Drug costs only</b>					
Costs	██████	██████	██	██████	██████
% change in TC:HDL	-41.0%	-17.5%	0%	-23.5%	-41.0%
<b>Incremental cost per 1% reduction in TC:HDL</b>				\$██████	\$██████
<b>Step 2: Time horizon extrapolated to 5 years</b>					
Costs	██████	██████	██	██████	██████
% change in TC:HDL	-41.0%	-17.5%	0%	-23.5%	-41.0%
<b>Incremental cost per 1% reduction in TC:HDL</b>				██████	██████
<b>Step 3: Transform outcomes to CHD events using trial-based patient and lipid characteristics, and Framingham risk equations. Include discount rate for drug costs. No discounting for outcomes</b>					
Costs	██████	██████	██	██████	██████
CHD events	0.1388	0.1744	0.1984	-0.0356	-0.0596
<b>Incremental cost per CHD event avoided</b>				██████	██████
<b>Step 4: Include familial hypercholesterolaemia risk multiplier</b>					
Costs	██████	██████	██	██████	██████
CHD events	0.3280	0.3993	0.4446	-0.0713	-0.1166
<b>Incremental cost per CHD event avoided</b>				██████	██████
<b>Step 5: Include additional costs associated with management of CHD events. Include discount rate for CHD event costs. No discounting for outcomes</b>					
Costs	██████	██████	██████	██████	██████
CHD events	0.3280	0.3993	0.4446	-0.0713	-0.1166
<b>Incremental cost per CHD event avoided</b>				██████	██████
<b>Step 6: Transform outcomes to LYs. Include discount rate for outcomes</b>					
Costs	██████	██████	██████	██████	██████
LYs	3.9639	3.8098	3.7085	0.1541	0.2554
<b>Incremental cost per LY gained</b>				\$██████	\$██████
<b>Step 7: Transform LYs to QALYs using disutility for CHD events</b>					
Costs	██████	██████	██████	██████	██████
QALYs	3.1859	3.0609	2.9786	0.1251	0.2073
<b>Incremental cost per QALY gained</b>				\$██████	\$██████
<b>Step 8: Modelled time horizon extrapolated to 35 years</b>					
Costs	██████	██████	██████	██████	██████
QALYs	6.4578	5.7202	5.2991	0.7376	1.1586
<b>Incremental cost per QALY gained</b>				██████	██████

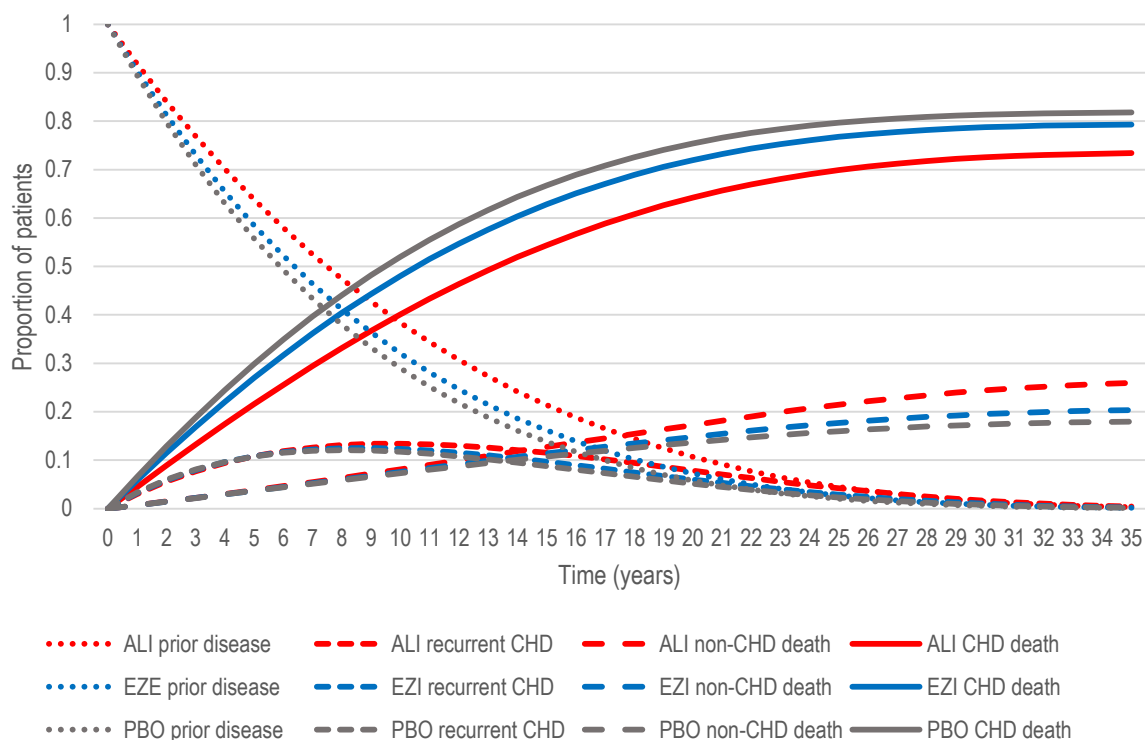
Source: Constructed during the evaluation based on data from the 'ALI\_model' Excel workbook  
 Abbreviations: CHD, coronary heart disease; HDL, high density lipoprotein; LYs, life years; TC, total cholesterol; QALYs, quality-adjusted life years

6.63 The transformation of TC:HDL outcomes to CHD events using modelled population characteristics, inclusion of the familial hypercholesterolaemia risk multiplier, transformation of CHD events to life years gained and the extrapolation of the

modelled time horizon to 35 years had the largest impacts on the stepped economic evaluations.

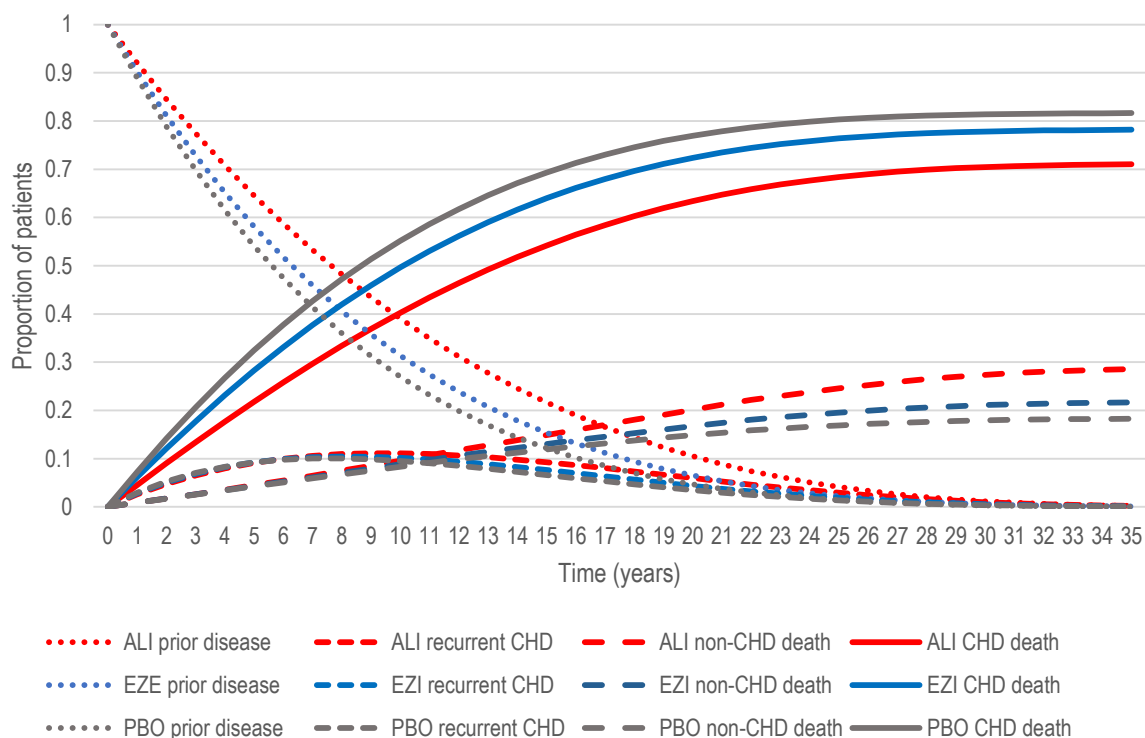
6.64 Markov traces constructed during the evaluation including the ezetimibe and placebo comparisons are summarised in Figure 1 (inadequate control on statin) and Figure 2 (statin intolerant) showing the proportion of patients remaining in each health state (prior atherosclerotic disease, recurrent CHD, CHD death and non-CHD death over the model duration.

**Figure 1: Markov trace of prior disease (baseline health state), recurrent CHD, non-CHD and CHD death (inadequate control on statin)**



Source: Constructed during the evaluation from the 'ALI\_model' Excel workbook of the submission  
 Abbreviations: ALI, alirocumab; CHD, coronary heart disease; EZE, ezetimibe; PBO, placebo

**Figure 2: Markov trace of prior disease (baseline health state), recurrent CHD, non-CHD death and CHD death (statin intolerant)**



Source: Constructed during the evaluation from the 'ALI\_model' Excel workbook of the submission  
 Abbreviations: ALI, alirocumab; CHD, coronary heart disease; EZE, ezetimibe; PBO, placebo

- 6.65 There were substantially more patients having any CHD event who experience CHD death compared to a relatively low proportion of non-fatal events (i.e. myocardial infarction or angina) in all treatment arms. Comparatively, there were much smaller differences in the proportion of non-fatal events between arms.
- 6.66 The modelled benefits associated with alirocumab treatment were primarily driven by the differences in CHD death compared with ezetimibe and placebo which appeared to have very little association with the differences in the proportion with non-fatal events between arms (i.e. when comparing the recurrent CHD with the CHD death model traces).
- 6.67 The submission did not attempt to validate the model traces using external sources of data.
- 6.68 The results of the sensitivity analyses indicate that the model is most sensitive to the time horizon, underlying cardiovascular risk (use of familial hypercholesterolaemia risk multiplier and adjustment for secondary prevention), utility estimates for the baseline health state (prior atherosclerotic disease) and population characteristics.

Table 10: Results of univariate sensitivity analyses

Univariate analysis	ICER (per QALY) vs ezetimibe	ICER (per QALY) vs placebo
<b>Inadequate control on statins</b>		
Base case	\$ [REDACTED]	\$ [REDACTED]
<b>Population characteristics</b>		
Risk factors and lipids from ODYSSEY COMBO II	\$ [REDACTED]	\$ [REDACTED]
Risk factors and lipids from BEACH SAND survey subgroup	\$ [REDACTED]	\$ [REDACTED]
Risk factors and lipids from Catapano (2016)	\$ [REDACTED]	\$ [REDACTED]
Risk factors and lipids from FH Retro	\$ [REDACTED]	\$ [REDACTED]
<b>Adjustment for secondary prevention increasing probability of CHD death</b>		
No adjustment	\$ [REDACTED]	\$ [REDACTED]
<b>Familial hypercholesterolaemia event rate multiplier (base case: 2.625)</b>		
1.0	\$ [REDACTED]	\$ [REDACTED]
1.5	\$ [REDACTED]	\$ [REDACTED]
2.0	\$ [REDACTED]	\$ [REDACTED]
<b>Utility for prior atherosclerotic disease, baseline health state (base case 0.8074)</b>		
Lower estimate (0.636)	\$ [REDACTED]	\$ [REDACTED]
Higher estimate (0.865)	\$ [REDACTED]	\$ [REDACTED]
<b>Model time horizon (base case: 35 years)</b>		
5 years	\$ [REDACTED]	\$ [REDACTED]
10 years	\$ [REDACTED]	\$ [REDACTED]
20 years	\$ [REDACTED]	\$ [REDACTED]
<b>Statin intolerant</b>		
Base case	\$ [REDACTED]	\$ [REDACTED]
<b>Adjustment for secondary prevention increasing probability of CHD death</b>		
No adjustment	\$ [REDACTED]	\$ [REDACTED]
<b>FH multiplier (base case 2.625)</b>		
1.0	\$ [REDACTED]	\$ [REDACTED]
1.5	\$ [REDACTED]	\$ [REDACTED]
2.0	\$ [REDACTED]	\$ [REDACTED]
<b>Utility for prior atherosclerotic disease, baseline health state (base case: 0.8074)</b>		
Lower estimate (0.636)	\$ [REDACTED]	\$ [REDACTED]
Higher estimate (0.865)	\$ [REDACTED]	\$ [REDACTED]
<b>Model time horizon (base case: 35 years)</b>		
5 years	\$ [REDACTED]	\$ [REDACTED]
10 years	\$ [REDACTED]	\$ [REDACTED]
20 years	\$ [REDACTED]	\$ [REDACTED]

Source: constructed during the evaluation using Table 3.9.1, p229 of the submission and 'ALI\_model' Excel workbook

Abbreviations: CHD, coronary heart disease; CL, confidence limit; FH, familial hypercholesterolaemia; HDL, high density lipoprotein; ICER, incremental cost-effectiveness ratio; incr, incremental; QALY, quality adjusted life year; TC, total cholesterol

The redacted table shows ICERs in the range of less than \$15,000/QALY – more than \$200,000/QALY.

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

**Drug cost/patient/year: \$ [REDACTED]**

6.69 The estimated annual drug cost for alirocumab was \$ [REDACTED] based on 13.04 scripts using the effective DPMQ \$ [REDACTED] for both the 75 mg and 150 mg fortnightly injections (based on ex-manufacturer prices and dispensing fees as of 1 July 2016). The increase in dispensing fees from 1 July 2017 has minimal impact on the economic analysis and financial estimates.

6.70 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***

6.71 This submission was considered by DUSC.

6.72 The submission used a combined market share/epidemiological approach to estimate the utilisation and financial implications associated with PBS listing of alirocumab for the treatment of HeFH and ASCVD over the first six years of listing. Estimates were based on effective prices.

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

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Year 6 (2023)
Projected utilisation of statin/ezetimibe treatments (patient-years)	████████	████████	████████	████████	████████	████████
Proportion with FH (1.1%)	████	████	████	████	████	████
Proportion with FH and CVD (27.9%)	████	████	████	████	████	████
Proportion with FH and CVD exceeding LDL target (2.6 mmol/L; 61.3%)	████	████	████	████	████	████
Expected uptake rates of alirocumab	57%	61%	66%	71%	75%	80%
<b>Predicted patient-years of alirocumab treatment</b>	████	████	████	████	████	████
Alirocumab scripts (13.04 per patient-year)	████████	████████	████████	████████	████████	████████
- 75 mg scripts (80%)	████████	████████	████████	████████	████████	████████
- 150 mg (20%)	████	████	████	████	████	████
Cost of alirocumab 75 mg and 150 mg (effective DPMQ: \$████████)	████████	████████	████████	████████	████████	████████
Patient copayments (\$13.56)	████████	████████	████████	████████	████████	████████
<b>Cost to the PBS/RPBS (DPMQ less copayments)</b>	████████	████████	████████	████████	████████	████████
Cost offset for substitution of ezetimibe	████████	████████	████████	████████	████████	████████
<b>Net cost to PBS/RPBS</b>	████████	████████	████████	████████	████████	████████

Source: Table 4.2.2, p241; Table 4.2.4, p242; Table 4.2.5, p243; Table 4.2.8, p246; Table 4.3.2, p248; Table 4.4.1, p249 of the submission

Abbreviations: CVD, cardiovascular disease; DPMQ, dispensed price maximum quantity; FH, familial hypercholesterolaemia; LDL, low density lipoprotein

The redacted table shows that at year 5, 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.

6.73 The DUSC considered the size of the eligible population presented in the submission to be underestimated, but uptake of alirocumab to be substantially overestimated. The main issues are:

- The number of patients eligible for alirocumab are likely to be underestimated because the market share approach:
  - doesn't account for people on alternative lipid lowering therapies that may be eligible for alirocumab; and
  - doesn't account for a potential increase in the market from earlier detection of FH or the availability of a new medicine class.
- The prevalence of CVD in patients with FH is uncertain as it is based on patients attending two lipid clinics and may not be representative of the eligible population for alirocumab. The AusDiab study may be a more appropriate source.

- The uptake of alirocumab in the eligible population (57% in Year 1 increasing to 80% in Year 6) is likely to be a substantial overestimate, based on uptake of injectable therapies in other chronic disease markets such as diabetes and osteoporosis.

### **Quality use of medicines**

6.74 The population with CVD is not homogenous. Factors identified as being important to support the safe and effective use of alirocumab did not address the different considerations for populations with the highest burden of CVD including Aboriginal and Torres Strait Islanders and those with mental illness.

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

## **7 PBAC Outcome**

7.1 The PBAC did not recommend alirocumab for patients with familial hypercholesterolaemia (FH) and clinical atherosclerotic cardiovascular disease (ASCVD) on the basis that the submission presented a very high and uncertain incremental cost effectiveness ratio and there was uncertainty around the size of the patient population and financial estimates. The PBAC noted the results of the ongoing ODYSSEY OUTCOMES trial, evaluating major adverse cardiac events (MACE) in individuals with hypercholesterolaemia, are due in early 2018.

7.2 The PBAC noted the high unmet clinical need for additional effective therapy for patients with FH and ASCVD. The PBAC considered that optimal dosing and up titration of statins remains a major QUM issue.

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 DLCNS of at least 6 appears reasonable, as the PBAC noted a score of 6–8 is considered probable FH.
- The PBAC noted the proposed LDL-c qualifying threshold of 2.6 mmol/L was not consistent with the available clinical evidence, treatment guidelines or current restrictions for ezetimibe. The Committee noted the argument that a threshold of 2.6 mmol/L would enable FH patients with ASCVD treated with alirocumab to potentially reach target levels of 1.8 mmol/L, but considered this threshold would potentially achieve even lower targets based on the evidence showing a 50-60% reduction compared to placebo and 20-30% compared to ezetimibe. The PBAC further noted the clinical evidence presented for the FH population had consistently higher mean baseline LDL-c (between 3.4 mmol/L and 5.1 mmol/L) and that for some patients the treatment goal is a 50% reduction in LDL-c rather than reaching the target level. The PBAC considered further modelling of the appropriate qualifying LDL-c threshold was required given the available clinical evidence and high estimated financial impact.
- The PBAC noted clinical 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 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 alirocumab 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 alirocumab, 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 PBAC also considered a secondary comparison with evolocumab as a near market comparator would have been informative.
- 7.5 The PBAC noted the key clinical trial evidence (presented in Section 6), based on a meta-analysis of seven randomised trials comparing alirocumab with placebo and four head-to-head randomised trials comparing alirocumab with ezetimibe, provided robust LDL-c data to support superior efficacy of alirocumab based on this surrogate, but no direct evidence for cardiovascular outcomes. The PBAC noted subgroup analyses suggested potential treatment effect modifiers (particularly by up-titration status), although no consistent treatment effect modification was seen.
- 7.6 The PBAC noted the ODYSSEY OUTCOMES trial is a large (n=18,600), ongoing trial evaluating major adverse cardiac events (MACE) in individuals with hypercholesterolaemia who have recently experienced acute coronary syndrome and are on background statin therapy. The PBAC considered the results of this trial, expected in early 2018, would provide additional clarity about the extent of cardiovascular benefit relative to their higher cost for this potentially widely used new therapy. The PBAC further considered an indirect comparison of alirocumab and evolocumab would be informative and could be performed using the ODYSSEY OUTCOMES and FORUIER trials.
- 7.7 The PBAC noted there are limited safety data beyond 18 months for alirocumab. Longer-term safety results are expected from the ODYSSEY OLE open-label extension study and the ODYSSEY OUTCOMES trial. The PBAC noted that while a lack of long-term safety data was previously a potential concern, there is no evidence of any safety signal of a very low LDL-c level. However, long-term drug specific safety concerns have not yet been addressed.
- 7.8 The PBAC noted the high and uncertain incremental cost-effectiveness ratio (ICER); \$45,000/QALY - \$75,000/QALY gained in the base case comparison with ezetimibe (in patients inadequately controlled on statins). The PBAC had concerns regarding the validity of the representative modelled populations given the small sample sizes with

which they are based upon, their baseline lipid levels and non-familial hypercholesterolaemia status. The PBAC also agreed with the ESC that the magnitude and timing of the assumed CV mortality benefit was likely overstated and a lag of 3-5 years in CV mortality may be reasonable based on published models (for example, Fonarow (2017)).

7.9 The PBAC noted the difficulties in estimating the eligible HeFH population and uptake as outlined by the DUSC and considered revised financial estimates would be required that take into account the issues raised from DUSC. The PBAC also considered a risk-share arrangement would be required that incorporates a cap on financial estimates to account for potential use in the non-FH population.

7.10 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**

Sanofi welcomes the PBAC's recognition of the high unmet clinical need for additional effective therapy for patients with familial hypercholesterolaemia and atherosclerotic cardiovascular disease and the benefits which alirocumab delivers with respect to clinically meaningful reductions in LDL-C, an outcome which is known to be associated with improvements in cardiovascular outcomes. Sanofi will continue to work with the PBAC to obtain reimbursement for alirocumab in patients with a high risk for cardiovascular events.