

## 7.01 ALIROCUMAB, 75 mg in 1 mL single dose pre-filled pen, 150 mg in 1 mL single dose pre-filled pen, Praluent<sup>®</sup>, Sanofi-Aventis

### 1 Purpose of Application

- 1.1 The resubmission requested a Section 85, Authority Required listing for alirocumab for treatment of heterozygous familial hypercholesterolaemia (he-FH) (patients with atherosclerotic disease or very high LDL levels); and non-familial hypercholesterolaemia (non-FH) in patients with a previous acute coronary syndrome (ACS), diabetes mellitus and elevated LDL levels.
- 1.2 The PBAC previously considered alirocumab at the November 2017 meeting for he-FH in patients with atherosclerotic disease and elevated LDL levels.
- 1.3 Listing was requested on a cost-minimisation basis versus evolocumab (for he-FH) and on a cost-effectiveness basis versus placebo (for non-FH and diabetes mellitus, post ACS).

**Table 1: Key components of the clinical issues addressed in the resubmission**

Population	Patients with he-FH who are not achieving target LDL levels despite treatment with maximum tolerated dose of a statin or who are statin-intolerant	Patients with non-familial hypercholesterolaemia with previous recent acute coronary syndrome and concomitant diabetes mellitus who are not achieving target LDL levels despite treatment with a maximum tolerated dose of a statin and ezetimibe, or who are statin-intolerant and treated with ezetimibe
Intervention	Alirocumab 75 mg subcutaneous injection fortnightly or 300 mg every 4 weeks, with potential up-titration to 150 mg fortnightly	
Comparator	Evolocumab subcutaneous injection 140 mg fortnightly or 420 mg once a month	Placebo
Outcomes	Reduction in LDL leading to reduction in cardiovascular events (e.g. cardiovascular death, myocardial infarction, angina) and quality of life	
Clinical claim	Alirocumab is non-inferior in terms of efficacy and safety compared to evolocumab	Alirocumab is superior in terms of efficacy and non-inferior in terms of safety compared to placebo

Source: Table 1.1.1, p2 of the resubmission

### 2 Requested listing

- 2.1 The resubmission requested a listing for he-FH patients with high cardiovascular risk (patients with atherosclerotic disease and/or very high LDL levels). The proposed listing has been amended from the November 2017 submission for he-FH with atherosclerotic disease, to align with the recommended PBS listing for evolocumab from March 2018. The extended PBS listing for evolocumab in familial heterozygous

hypercholesterolaemia was effective from 1 November 2018. The alirocumab restriction would need to align with this listing.

- 2.2 The resubmission also requested a new listing for the treatment of non-FH patients with ACS and diabetes.
- 2.3 The resubmission requested a grandfathering provision for patients currently treated with alirocumab if they previously met the eligibility criteria in the proposed restrictions. Neither of the proposed grandfathering restrictions have strict definitions of statin intolerance nor require prior ezetimibe treatment.
- 2.4 Suggestions and additions proposed by the Secretariat to the requested listing clinical criteria for the He-FH indication are added in italics and suggested deletions are crossed out with strikethrough. The Secretariat did not provide suggested changes to the non-FH indication.

***Heterozygous familial hypercholesterolaemia (he-FH)***

Name, Restriction, Manner of administration and form	Max. Qty (pack)	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
ALIROCUMAB 75mg/mL injection, 2 x 1mL pre-filled pen	1	5	\$ [REDACTED]	Praluent	Sanofi-Aventis
ALIROCUMAB 150mg/mL injection, 2 x 1mL pre-filled pen	1	5	\$ [REDACTED]	Praluent	Sanofi-Aventis

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	Chronic
<b>Condition:</b>	<del>Heterozygous familial hypercholesterolaemia</del>
<b>PBS Indication:</b>	<del>Heterozygous</del> Familial <del>heterozygous</del> hypercholesterolaemia
<b>Treatment phase:</b>	Initial 4 <i>treatment</i>
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required – Electronic <input type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>The treatment must be in conjunction with dietary therapy and exercise, <b>AND</b>  <del>The treatment must be in conjunction with other lipid lowering therapy</del>  <b>AND</b>            The condition must have been confirmed by genetic testing; <b>OR</b>            The condition must have been confirmed by a Dutch Lipid Clinic Network Score of at least 6, <b>AND</b>            Patient must have an LDL cholesterol level in excess of <del>5 millimoles per litre, or</del> 3.3 millimoles per litre in the presence of <del>established</del> <i>symptomatic</i> atherosclerotic cardiovascular disease; <b>OR</b>  <i>Patient must have an LDL cholesterol level in excess of 5 millimoles per litre,</i></p>

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	<p><del>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</del> <b>AND</b>  <i>Patient must have been treated with the maximum recommended dose of atorvastatin or rosuvastatin according to the TGA-approved Product Information for at least 3 months in conjunction with dietary therapy and exercise; OR</i>  <i>Patient must have developed clinically important product-related adverse events necessitating withdrawal of statin treatment to trials of each of atorvastatin and rosuvastatin; OR</i>  <i>Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information, AND</i>  <i>Patient must have been treated with ezetimibe for at least 3 months in conjunction with dietary therapy and exercise.</i></p> <p><del>Patient must have an LDL cholesterol level in excess of 5 millimoles per litre, or 3.3 millimoles per litre in the presence of established atherosclerotic cardiovascular disease, after having developed a clinically important product-related adverse event after a trial of treatment with at least 2 different HMG CoA reductase inhibitors (statins) necessitating a withdrawal of statin treatment; OR</del>  <del>Patient must have an LDL cholesterol level in excess of 5 millimoles per litre, or 3.3 millimoles per litre in the presence of established atherosclerotic cardiovascular disease, and must be one in whom treatment with an HMG CoA reductase inhibitor (statin) is contraindicated.</del></p>
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**Non-Familial hypercholesterolaemia (non-FH) with acute coronary syndrome (ACS) and diabetes**

Category/Program	General Schedule
PBS Indication	Hypercholesterolaemia
Restriction	Authority Required – In Writing
Clinical criteria	<p>The treatment must be in conjunction with dietary therapy and exercise</p> <p>AND</p> <p>The treatment must be in conjunction with other lipid lowering therapy</p> <p>AND</p> <p>Patient must have been hospitalised for an acute myocardial infarction; OR          Patient must have been hospitalised for unstable angina</p> <p>AND</p> <p>Patient must have diabetes mellitus</p> <p>AND</p> <p>Patient must have an LDL cholesterol level in excess of 2.59 millimoles per litre after at least 3 months of treatment at a maximum tolerated dose of an HMG CoA reductase inhibitor (statin) plus ezetimibe, in conjunction with dietary therapy and exercise; OR</p> <p>Patient must have an LDL cholesterol level in excess of 2.59 millimoles per litre after at least 3 months of treatment with ezetimibe, and have developed a clinically important product-related adverse event after a trial of treatment with at least 2 different HMG CoA reductase inhibitors (statins) necessitating a withdrawal of statin treatment; OR</p> <p>Patient must have an LDL cholesterol level in excess of 2.59 millimoles per litre after at least 3 months of treatment with ezetimibe, and must be one in whom treatment with an HMG CoA reductase inhibitor (statin) is contraindicated.</p>

- 2.5 The resubmission proposed a special pricing arrangement consisting of a [REDACTED] % rebate on government expenditure. This is a larger rebate than previously proposed for he-FH with clinical atherosclerotic cardiovascular disease ([REDACTED] % rebate from previous published price of \$[REDACTED], November 2017 submission).
- 2.6 The resubmission proposed flat pricing between the dose strengths. This pricing structure remains unchanged from the November 2017 submission, however, no additional justification in terms of dose equivalence was provided in the resubmission.
- 2.7 The recommended starting dose in the product information is either 75 mg fortnightly or 300 mg every 4 weeks. Under the proposed listing, it is possible to administer the starting dose using either preparation (i.e. the 75 mg or 150 mg). If additional LDL reduction is required, the dosage may be adjusted to the maximum dosage of 150 mg once every 2 weeks.
- 2.8 The full restrictions also include treatment criteria identifying patients with statin intolerance. This was defined as a trial of at least 2 statins at the maximum tolerated dose and documented clinically important treatment-related adverse events, which was consistent with the current evolocumab restriction for familial disease.
- 2.9 The requested restriction narrows the eligible population to a small subset of patients with higher overall cardiovascular risk (i.e. he-FH with lipid levels that are inadequately controlled and/or atherosclerotic cardiovascular disease; or non-FH with prior ACS AND diabetes) compared with the TGA approved indication which covers a broader hypercholesterolaemia population (i.e. he-FH OR non-familial clinical atherosclerotic cardiovascular disease).
- 2.10 There is potential for alirocumab to be used outside the approved TGA indication in patients with homozygous familial hypercholesterolaemia as the clinical criterion of a Dutch Lipid Clinic Network Score of at least 6 does not differentiate between homozygous and heterozygous disease. There are ongoing trials for alirocumab 150 mg fortnightly only in adults and children/adolescents with homozygous familial hypercholesterolaemia (ODYSEY HoFH expected completion January 2019; NCT03510715, expected completion June 2020). The ESC considered there would not be significant prescriber confusion and the risk of use in homozygous patients was small, given the low patient numbers and the PBS indication specifying 'heterozygous' patients.
- 2.11 The resubmission used the subset of non-FH patients with previous ACS and diabetes as the subpopulation at higher risk of cardiovascular events, without providing adequate justification for this subgroup, given there are other subpopulations who are also at high risk of cardiovascular events. The current PBS listing for ezetimibe identifies other subgroups with high cardiovascular risk including patients with cerebrovascular disease, Aboriginal and Torres Strait Islanders with diabetes and patients with a family history of coronary heart disease. The resubmission did not consider these other subgroups. The ESC considered the proposed listing for this population to be complex and advised that the PBAC consider whether other higher

risk categories would better define the optimal population for intervention across the PCSK9-inhibitor class of drugs.

- 2.12 The proposed LDL thresholds for familial ( $\leq 3.3$  or  $\leq 5$  mmol/L; same as the current listing for evolocumab) and non-familial disease ( $<2.6$  mmol/L) are inconsistent with key trial evidence which generally used lower LDL thresholds (the ODYSSEY OUTCOMES trial specified a qualifying LDL threshold of  $\geq 1.8$  mmol/L for patients with a recent ACS). Current treatment guidelines typically suggest more aggressive treatment targets for patients with atherosclerotic disease (e.g. LDL  $< 1.8$  mmol/L) and patients with familial hypercholesterolaemia without atherosclerotic disease (LDL  $< 2.6$  mmol/L). The ESC noted a potential gap exists for individuals who fail to achieve target LDL on a maximum tolerated dose statin and trial of ezetimibe, but who are not eligible for alirocumab. The ESC further noted that the chosen LDL thresholds were defined based on prior PBAC decisions (in regard to evolocumab in the ho-FH and he-FH populations) and potential cost-effectiveness and were not guideline driven.
- 2.13 There are multiple differences between the PCSK9 inhibitors in terms of TGA approved indications, and PBS requested restrictions that may be confusing to prescribers. The ESC advised the terminology used between the PCSK9 inhibitor restrictions should be consistent and that there was consistency in the restrictions between the PCSK9 inhibitors for the same indications.

*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 one or more of: he-FH, clinical atherosclerotic cardiovascular disease or hypercholesterolaemia with high or very high cardiovascular risk.
- In combination with a statin, or statin with other lipid-lowering therapies in patients unable to reach LDL goals with a maximum tolerated dose of statin or,
  - In combination with other lipid-lowering therapies in patients who are statin-intolerant or contraindicated who are unable to reach LDL goals.

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

- 3.2 The sponsor was also seeking a revision of the TGA indication to include a broader population at the time of this submission. [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

***Previous PBAC consideration***

3.4 The outstanding matters of concerns from the previous November 2017 PBAC meeting (for he-FH) are summarised in the table below.

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

**Table 2: Summary of outstanding matters of concern**

Matter of concern	How the resubmission addresses it
<p>The PBAC did not recommend alirocumab for patients with familial hypercholesterolaemia (FH) and clinical atherosclerotic cardiovascular disease (ASCVD) on the basis of a very high and uncertain incremental cost effectiveness ratio and uncertainty around the size of the patient population and financial estimates [7.1 November 2017 PSD]</p>	<p>The resubmission proposed a reduction in the effective price of alirocumab from \$ [redacted] (based on a [redacted]% rebate from the November 2017 published price \$ [redacted]) to \$ [redacted] (based on a [redacted]% rebate from the published price \$ [redacted]).</p> <p>The resubmission conducted a cost-minimisation analysis versus evolocumab for FH.</p>
<p>There is a high unmet clinical need for additional effective therapy for patients with FH and ASCVD. The optimal dosing and up titration of statins remains a major QUM issue [7.2 November 2017 PSD]</p>	<p>The resubmission has revised the requested restriction for FH to align with the current listing for evolocumab (updated LDL qualifying thresholds, diagnostic criteria, statin intolerance and use of alirocumab as monotherapy).</p>
<p>The proposed Authority Required (written) restriction was complex as there are multiple considerations required to define a potentially cost-effective population. Key issues include diagnostic criteria, LDL qualifying thresholds, definition of atherosclerotic disease, definition of statin intolerance and use of alirocumab as monotherapy [7.3 November 2017 PSD]</p>	<p>The requested listing for non-FH patients was for patients with ACS and diabetes. In the July 2018 rejection of evolocumab in non-FH, the ESC noted high risk subgroups (e.g. those with more recent MI, multiple prior MIs and residual multi-vessel coronary artery disease) identified in a published analysis of the FOURIER trial (Sabatine, 2018) as likely to receive a greater benefit from treatment with evolocumab [2.7 July 2018 PSD, evolocumab]. Also, the current PBS listing for ezetimibe identifies other subgroups with high cardiovascular risk including patients with cerebrovascular disease, Aboriginal and Torres Strait Islanders with diabetes and patients with a family history of coronary heart disease.</p>
<p>The nominated comparators of ezetimibe and placebo were appropriate. The PBAC also considered a secondary comparison with evolocumab as a near market comparator would have been informative [7.4 November 2017 PSD]</p>	<p>The resubmission proposed evolocumab as the main comparator for FH.</p> <p>The resubmission nominated placebo as the main comparator for non-FH. An ITC against evolocumab was performed.</p>
<p>The key clinical trial evidence based on lipid trials comparing alirocumab with placebo or ezetimibe provided robust 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 [7.5 November 2017 PSD]</p>	<p>The resubmission presented cardiovascular outcome data with alirocumab versus placebo from the ODYSSEY OUTCOMES trial.</p>
<p>The ODYSSEY OUTCOMES trial is a large (n=18,600) cardiovascular outcomes trial in hypercholesterolaemia patients who have recently experienced acute coronary syndrome and are on background statin therapy. The results of this trial 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 FOURIER trials [7.6 November 2017 PSD]</p>	<p>The resubmission presented an indirect comparison of alirocumab and evolocumab based on the ODYSSEY OUTCOMES and FOURIER trials. Supportive analyses were presented based on an indirect comparison of lipid trials of alirocumab and evolocumab in familial hypercholesterolaemia populations.</p>

Matter of concern	How the resubmission addresses it
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 [7.7 November 2017 PSD]	The resubmission presented safety data from the ODYSSEY OLE extension study and the ODYSSEY OUTCOMES trial.
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 [7.9 November 2017 PSD]	The resubmission presented revised financial estimates using an epidemiology approach and new sources of data. The resubmission proposed a risk-share arrangement to address concerns around leakage (no details were provided).

Source: Table 1.1.5, pp23-24; Table 3.2.1, p185; Table 4.1.1, p218 of the resubmission; Abbreviations: LDL, low density lipoprotein; QUM, quality use of medicines

## 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 he-FH with very high LDL levels OR non-FH with prior ACS and concomitant diabetes.
- 4.3 The resubmission claimed that alirocumab would replace evolocumab in the he-FH population, or be used in addition to statins and/or non-statin therapies.
- 4.4 The positioning of alirocumab as a third-line treatment option in addition to a statin and ezetimibe was consistent with the recently published American College of Cardiology/American Heart Association Task Force 2018 Guideline on the Management of Blood Cholesterol.
- 4.5 There were inconsistencies in LDL targets in the proposed algorithm at each line of therapy ranging from <1.8 mmol/L to <5 mmol/L. Therapeutic targets in more recently published guidelines are substantially lower than the LDL criteria outlined in the requested restriction. As a consequence, there is likely to be a substantial pool of patients who are not achieving target LDL levels with existing therapies but who would not be eligible for PBS-subsidised treatment with alirocumab.

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

## 5 Comparator

- 5.1 The resubmission nominated evolocumab as the main comparator in patients with he-FH. The ESC considered evolocumab to be the appropriate main comparator for this population.
- 5.2 The resubmission nominated placebo as the main comparator in patients with non-FH with previous recent ACS and concomitant diabetes. The ESC considered this

comparator to be reasonable. The resubmission claimed that patients in this high risk subgroup who are on multiple existing therapies (e.g. statin + ezetimibe + other lipid lowering therapy) and who are unable to achieve target LDL levels have no other treatment options. For the non-familial population, the PBAC previously considered that treatment with evolocumab must be in conjunction with the maximum tolerated dose of a statin and ezetimibe unless contraindicated (para 2.3, evolocumab Public Summary Document (PSD) July 2018).

- 5.3 The resubmission did not consider evolocumab as a potential near market comparator, arguing that evolocumab was not previously considered by the PBAC for non-FH in the subset with previous ACS and diabetes. The Commentary considered evolocumab should be considered a near market comparator given the PBAC has previously considered evolocumab for the non-FH population with atherosclerotic cardiovascular disease (evolocumab November 2017 and July 2018 PSDs), which has substantial overlapping indications with the proposed target population for alirocumab. The ESC agreed with the Commentary and advised that the indirect treatment comparison (ITC) of the CV outcomes trials, in patients with non-FH, was informative.

*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 (6) 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 greatly reduce the risk of cardiovascular events for patients with familial hypercholesterolaemia through achieving target lipid levels. The Familial Hypercholesterolaemia Family Support Group of Western Australia (FHSG) also emphasised the high need for PCSK9 inhibitors as a treatment alternative for patients who are statin intolerant.

### ***Clinical trials***

- 6.3 The resubmission was based on a series of comparisons of alirocumab and nominated comparators. These analyses have not previously been considered by the PBAC:
- Indirect comparison of cardiovascular outcomes with alirocumab versus evolocumab in predominantly non-FH populations with high cardiovascular risk (ODYSSEY OUTCOMES, FOURIER).
  - Post-hoc subgroup analyses of cardiovascular outcomes with alirocumab versus placebo in patients with diabetes and LDL  $\geq 2.6$  mmol/L (ODYSSEY OUTCOMES).

- Supportive analyses based on an indirect comparison of lipid outcomes with alirocumab versus evolocumab in he-FH populations (FH I, FH II, RUTHERFORD I, RUTHERFORD II). The resubmission did not adequately justify the exclusion of the ESCAPE, HIGH FH and Stein 2012 trials of alirocumab in heterozygous familial populations which include dosing regimens requested for reimbursement (previously considered by the PBAC in the November 2017 submission). These trials were included in alternative analyses during the evaluation.

6.4 Details of the included trials are provided in the table below.

**Table 3: Trials and associated reports of included trials**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Alirocumab clinical trials</b>		
ESCAPE	Moriarty PM, Parhofer KG, Babirak SP et al (2016). Alirocumab in patients with heterozygous familial hypercholesterolaemia undergoing lipoprotein apheresis: the ODYSSEY ESCAPE trial.	European Heart Journal, 37: 3588-3595
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
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
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 OUTCOMES	Sanofi Clinical Study Report (2018). A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effect of SAR236553/REGN727 on the Occurrence of Cardiovascular Events in Patients Who Have Recently Experienced an Acute Coronary Syndrome.	Internal study report
	Schwartz GG, Bessac L, Berdan LG 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(5):682-9
	Schwartz GG, Steg PG, Szarek M et al (2018). Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome.	New England Journal of Medicine (early online publication), DOI: 10.1056/NEJMoa1801174
Stein 2012 (CL1003)	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

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Trial ID	Protocol title/ Publication title	Publication citation
<b>Evolocumab clinical trials</b>		
FOURIER (20110118)	Sabatine MS et al (2015). Rationale and design of the Further cardiovascular Outcomes Research with PCSK9 Inhibition in subjects with Elevated Risk trial.	American Heart Journal 173: 94-101
	Sabatine MS et al (2017). Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease	New England Journal of Medicine, 376: 1713-1722
RUTHERFORD-1 (20090158)	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 with PCSK9 inhibition in heterozygous familial hypercholesterolaemia disorder (RUTHERFORD) randomized trial	Circulation, 126: 2408–2417
RUTHERFORD-2 (20110117)	Raal F et al (2015). PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial.	Lancet 9965: 331–340

Source: Table 2.2.3, pp69-71 of the resubmission, clinical trial reports and publications  
*Studies in italics were identified but not presented in the resubmission*

6.5 The key features of the included trials are summarised in the table below.

**Table 4: Key features of the included evidence**

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Alirocumab trials</b>						
ESCAPE	62	MC, R, DB, PC 18 weeks	Low	HeFH undergoing LDL apheresis	Rate of apheresis treatments	Not used
FH I	486	MC, R, DB, PC 78 weeks	Low	HeFH	Change in LDL levels	Not used
FH II	249	MC, R, DB, PC 78 weeks	Low	HeFH	Change in LDL levels	Not used
HIGH FH	107	MC, R, DB, PC 78 weeks	Unclear	HeFH with high LDL levels	Change in LDL levels	Not used
ODYSSEY OUTCOMES	18,924	MC, R, DB, PC Median follow-up of 2.8 years	Low	Hypercholesterolaemia with recent ACS event	Cardiovascular events, lipid parameters	Used
Stein 2012	77	MC, R, DB, PC 5 treatment arms 12 weeks	Low	HeFH	Change in LDL levels	Not used
<b>Evolocumab trials</b>						
FOURIER	27,564	MC, R, DB, PC Approximately 2 year duration	Low	Hypercholesterolaemia with atherosclerotic disease	Cardiovascular events, lipid parameters	Not used
RUTHERFORD-1	167	MC, R, DB, PC 12 weeks	Low	HeFH	Change in LDL levels	Not used
RUTHERFORD-2	329	MC, R, DB, PC 12 weeks	Low	HeFH	Change in LDL levels	Not used

Source: Compiled during the evaluation using pp78-93 of the resubmission, clinical trial reports and trial publications

Abbreviations: ACS, acute coronary syndrome; DB, double blind; LDL, low density lipoprotein cholesterol; MC, multi-centre; PC, placebo-controlled; R, randomised.

### **Comparative effectiveness**

6.6 Key cardiovascular outcomes reported in the ODYSSEY OUTCOMES trial are summarised in the table below.

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

Outcome	Alirocumab N = 9462	Placebo N = 9462	Hazard ratio (95% CI)	Hierarchical P-value
<b>Composite outcomes (first event only)</b>				
Time to coronary death, non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, or unstable angina requiring hospitalisation [primary outcome]	903 (9.5%)	1052 (11.1%)	<b>0.85 (0.78, 0.93)</b>	<b>&lt;0.001</b>
Time to coronary death, non-fatal myocardial infarction, unstable angina requiring hospitalisation, or ischaemia-driven coronary revascularisation	1199 (12.7%)	1349 (14.3%)	<b>0.88 (0.81, 0.95)</b>	<b>0.001</b>
Time to coronary death and non-fatal myocardial infarction	793 (8.4%)	899 (9.5%)	<b>0.88 (0.80, 0.96)</b>	<b>0.006</b>
Time to cardiovascular death, non-fatal myocardial infarction, non-fatal ischaemic stroke, unstable angina requiring hospitalisation, or ischaemia-driven coronary revascularisation	1301 (13.7%)	1474 (15.6%)	<b>0.87 (0.81, 0.94)</b>	<b>&lt;0.001</b>
Time to death from any cause, non-fatal myocardial infarction, or non-fatal ischaemic stroke	973 (10.3%)	1126 (11.9%)	<b>0.86 (0.79, 0.93)</b>	<b>&lt;0.001</b>
<b>Individual outcomes</b>				
Time to coronary death	205 (2.2%)	222 (2.3%)	0.92 (0.76, 1.11)	0.38 <sup>a</sup>
Time to cardiovascular death	240 (2.5%)	271 (2.9%)	0.88 (0.74, 1.05)	-
Time to death from any cause	334 (3.5%)	392 (4.1%)	0.85 (0.73, 0.98)	-
Time to non-fatal myocardial infarction	626 (6.6%)	722 (7.6%)	0.86 (0.77, 0.96)	-
Time to fatal or non-fatal myocardial infarction	646 (6.8%)	756 (8.0%)	0.85 (0.76, 0.94)	-
Time to fatal or non-fatal ischaemic stroke	111 (1.2%)	152 (1.6%)	0.73 (0.57, 0.93)	-
Time to unstable angina requiring hospitalisation	37 (0.4%)	60 (0.6%)	0.61 (0.41, 0.92)	-
Time to ischaemia-driven coronary revascularisation	731 (7.7%)	828 (8.8%)	0.88 (0.79, 0.97)	-
Time to hospitalisation for congestive heart failure	176 (1.9%)	179 (1.9%)	0.98 (0.79, 1.20)	-

Source: Table 2.5.1, p99 and Table 2.5.4, p102 of the resubmission; Table 16.2.6.2.13.1 of the clinical trial report and Table 2, p7 of the Schwartz et al (2018) trial publication

Abbreviation: CI, confidence interval

<sup>a</sup> The hierarchical analysis was stopped after the first non-significant p-value was observed.

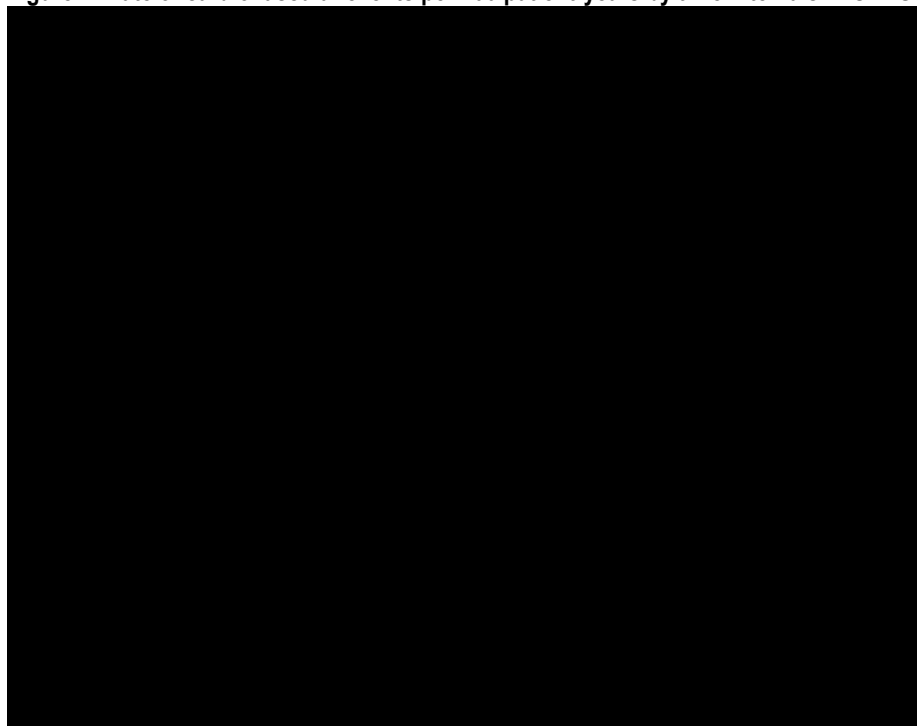
Results in bold were statistically significant

- 6.7 Treatment with alirocumab was associated with a decreased risk of death from any cause, myocardial infarction, fatal or non-fatal ischaemic stroke, hospitalised unstable angina and ischaemia-driven coronary revascularisation compared to placebo. These results should be interpreted with caution given the hierarchical testing was stopped after a non-statistically significant result for time to coronary death and confidence intervals were not adjusted for multiplicity.
- 6.8 There was no apparent difference in coronary death, cardiovascular death and hospitalised congestive heart failure between treatment arms.
- 6.9 The results of the ODYSSEY OUTCOMES trial were broadly consistent with the results from the FOURIER trial, which recruited stable patients without a recent ACS event. In both trials, treatment with PCSK9 inhibitors was associated with decreased risks of

myocardial infarction, stroke and coronary revascularisation compared to placebo; and neither trial showed an apparent difference in cardiovascular death between treatment arms.

- 6.10 Figure 1 presents an analysis of time to coronary death, non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, or unstable angina requiring hospitalisation by time intervals for the whole trial population.

**Figure 1: Rate of cardiovascular events per 100 patient-years by time intervals in ODYSSEY OUTCOMES**



Source: Figure 16.2.6.1.2.2 (section 16.2.6) of the clinical trial report

- 6.11 The results suggest that alirocumab is associated with a decrease in the rate of cardiovascular events compared with placebo. The curves indicate divergence by 6 months with peak difference at approximately 18 months and convergence towards the end of the trial. The Pre-Sub-Committee response (PSCR) argued the convergence in the rate of cardiovascular events between arms in the ODYSSEY OUTCOMES trial should be interpreted with caution given the relatively small number of patients contributing to the data at 4 years (6.8% of the total cohort). The ESC noted the uncertainty with the data at 4 years, however also noted the curves started to converge from 18 months and a relatively large number of patients remained at risk between 2–3 years. A similar pattern of convergence was also seen with LDL reduction. The ESC felt that this may not have been adequately explained by down titration of alirocumab therapy to maintain an LDL-c range nor by the fewer numbers of patients followed up to 4 years.
- 6.12 A separate analysis by time interval indicated no apparent difference in cardiovascular events with alirocumab treatment in the first year (HR 0.94, 95% CI 0.83, 1.08). There was a relative decrease in cardiovascular events in the alirocumab arm compared with

the placebo arm in subsequent years (HR 0.77, 95% CI 0.69, 0.87). This analysis indicates that there may be a time lag between the initiation of alirocumab therapy and the accrual of cardiovascular benefits which is consistent with the landmark analysis for the FOURIER trial.

- 6.13 LDL results from the ODYSSEY OUTCOMES trial suggest attenuation in LDL reduction over time associated with alirocumab versus placebo with 60.1% change from baseline observed at Month 4, which decreased over time to 53.7% at Month 12 and to 39.9% at Month 48. In the FOURIER trial, treatment with evolocumab was associated with a 59% relative decrease in LDL levels compared to placebo, which was sustained over approximately 3 years.
- 6.14 The resubmission claimed that the attenuation in LDL reduction may be due to the dosing algorithm that allowed for down-titrations and/or switching to placebo and the use of LDL targets (between 0.78 to 1.29 mmol/L) which was different to previous trials of alirocumab with lipid outcomes. The PSCR indicated that there were 805/9,451 patients (8.5%) treated with alirocumab 150 mg fortnightly who had their dose down-titrated to 75 mg fortnightly, and 730 patients (7.7%) patients treated with alirocumab 75 mg fortnightly who were switched to placebo. The ODYSSEY OUTCOMES trial did not report LDL reductions by titration status.
- 6.15 The PBAC previously noted that there was an approximate 20% difference in LDL reduction observed in subgroup analyses of patients receiving alirocumab who were up-titrated compared to those with no titration (para 7.5, alirocumab November 2017 PSD). Data from an exploratory analysis of the open label extension (OLE) study suggest a similar difference in LDL reduction due to alirocumab titration.
- 6.16 Overall, the magnitude of cardiovascular risk reduction associated with alirocumab is likely to differ depending on baseline cardiovascular risk and LDL levels. The PBAC previously considered the strength of association between LDL levels and cardiovascular outcomes to be robust and consistent with the extensive body of evidence, however, stated that the results from the ODYSSEY OUTCOMES trial would also be informative (para 6.49, alirocumab PSD November 2017).
- 6.17 Results from the ODYSSEY OUTCOMES trial report suggest a 25% reduction in cardiovascular risk per 1 mmol/L decrease in LDL with alirocumab treatment (HR 0.75, 95% CI 0.72, 0.78). The trial report noted that this was consistent with Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis that suggested a 22% risk reduction per 1 mmol/L decrease in LDL. The results were also broadly consistent with landmark analyses from the FOURIER trial suggesting relative risk reductions in major coronary events per 1 mmol/L reduction in LDL (Year 1: HR 0.87, 95% CI 0.79, 0.97; Year 2: HR 0.80, 95% CI 0.71, 0.90; reported in Sabatine 2017).

### ***Subgroup analyses***

- 6.18 The resubmission conducted post-hoc analyses of the combined subgroup with diabetes and LDL  $\geq 2.6$  mmol/L for the primary composite outcome and for MACE without stroke from the ODYSSEY OUTCOMES trial summarised in the table below.

The resubmission did not adequately justify the use of a post-hoc composite outcome of MACE without stroke (defined as coronary death, fatal or non-fatal myocardial infarction or unstable angina requiring hospitalisation) in the economic model. The PBAC noted that the HR for ischaemic stroke reduction was, in fact, better than the overall HR for the MACE definition that was used in the model.

**Table 6: Subgroup analyses results of diabetes and LDL  $\geq$ 2.6 mmol/L from the recent ACS population of the ODYSSEY OUTCOMES trial**

Outcome	Alirocumab	Placebo	Hazard ratio (95% CI)	Interaction p-value
<b>Time to coronary death, non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, or unstable angina requiring hospitalisation [primary outcome]</b>				
Overall (N = 18,924)	903 (9.5%)	1052 (11.1%)	0.85 (0.78, 0.93)	-
Diabetes and LDL $\geq$ 2.6 mmol/L (N = [redacted])	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted], [redacted])	[redacted]
Complement [LDL <2.6 mmol/L, no diabetes and LDL $\geq$ 2.6 mmol/L] (N = 17,345)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted], [redacted])	
<b>Time to coronary death, fatal or non-fatal myocardial infarction, or unstable angina requiring hospitalisation [without stroke]</b>				
Overall (N = 18,924)	814 (8.6%)	941 (9.9%)	0.86 (0.78, 0.94)	-
Diabetes and LDL $\geq$ 2.6 mmol/L (N = 1,579)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted], [redacted])	[redacted]
Complement [LDL <2.6 mmol/L, no diabetes and LDL $\geq$ 2.6 mmol/L] (N = 17,345)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted], [redacted])	
<b>Time to coronary death</b>				
Overall (N = 18,924)	205 (2.2%)	222 (2.3%)	0.92 (0.76, 1.11)	-
Diabetes and LDL $\geq$ 2.6 mmol/L (N = 1,579)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted], [redacted])	[redacted]
Complement [LDL <2.6 mmol/L, no diabetes and LDL $\geq$ 2.6 mmol/L] (N = 17,345)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted], [redacted])	

Source: Table 4.3.1.1 to 4.3.4.3, pp108-124 of ODYSSEY additional subgroup analyses\_diabetes + LDL 2.6, Attachment 7 of the resubmission

Abbreviations: CI, confidence interval; NR, not reported

Results highlighted in grey were used in the economic model

*Italics: provided in the PSCR, Table 1, p3.*

6.19 Subgroup analyses in patients with recent ACS, diabetes and LDL  $\geq$ 2.6 mmol/L indicated that treatment with alirocumab was associated with decreased risks of cardiovascular events compared to placebo based on key composite outcomes. The results suggest greater relative treatment effect with alirocumab in this subgroup compared to the whole trial population. These results should be interpreted with caution due to this being an underpowered trial sub-group analysis, no significant heterogeneity identified between the subgroup and the overall group (overlapping confidence intervals), and potential confounding, and small patient numbers (and events) relative to its complement. The evaluation considered that although the absolute risk reduction observed in this subgroup is likely to be greater than the whole trial population, it is unlikely that the combination of diabetes and elevated LDL levels is a treatment effect modifier. The PSCR provided an analysis to support a higher relative treatment effect with alirocumab in this modelled non-FH population, but the

ESC noted the hazard ratios and confidence intervals showed overlap with the ITT population indicating that there is still some uncertainty. The PSCR acknowledged that post-hoc analyses introduce a level of bias, but noted the previous PBAC feedback that reimbursement for a non-FH population should be confined to a small, high risk patient group, and that these analyses were done to demonstrate where the greatest cost-effectiveness of alirocumab could be achieved. The ESC agreed that post-hoc analyses were necessary to define an appropriate population but considered it remained uncertain whether the particular subgroup identified (prior ACS, diabetes with LDL >2.59mmol/L) represents the most appropriate higher risk group or whether other higher risk categories would better define the optimal population for intervention with alirocumab.

- 6.20 There was no apparent difference in coronary death between treatment arms. This was consistent with results from the whole trial population, and with the FOURIER trial for evolocumab.
- 6.21 The PBAC previously considered results from high risk subgroups identified in Sabatine (2018) among patients with more recent myocardial infarction, multiple prior myocardial infarctions or residual multi-vessel coronary artery disease from the FOURIER trial (para 6.11, evolocumab PSD July 2018). These subgroups were at a higher risk of cardiovascular events and achieved greater cardiovascular risk reductions with evolocumab treatment compared to their complement subgroups.
- 6.22 The overall trend in LDL levels and TC:HDL ratio in the subgroup of patients with diabetes and LDL  $\geq 2.6$  mmol/L appeared consistent with results for the whole trial population (greatest reduction at Month 4 then decreasing over time). As expected, absolute change in each of the lipid parameters was greater in the subgroup than observed in the whole trial population due to higher baseline lipid levels. Results for TC:HDL ratio were used as inputs in the economic model.
- 6.23 Quality of life data from the ODYSSEY OUTCOMES trial suggested no statistically significant differences in EQ-5D scores from baseline to Month 42 between alirocumab and placebo. Descriptive results from the subgroup with diabetes and elevated LDL in the economic model were consistent with the broader trial population.

***Indirect comparison***

- 6.24 An overall summary of the indirect analyses comparing alirocumab and evolocumab based on the ODYSSEY OUTCOMES and FOURIER trials is presented in the table below. The ESC considered the ITC of the CV outcomes trials in the non-familial population to be informative, but for establishing equi-effective doses in the heterozygous familial

population, the ITC based on the lipid trials were of increased relevance given they were conducted in the population of interest.

**Table 7: Indirect analyses comparing alirocumab with evolocumab based on cardiovascular outcomes**

Trial	Alirocumab, n/N (%)	Placebo, n/N (%)	Evolocumab, n/N (%)	HR (95% CI)
<b>Time to coronary death, non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, or unstable angina requiring hospitalisation (ODYSSEY OUTCOMES); or Time to cardiovascular death, myocardial infarction, stroke, unstable angina requiring hospitalisation, or coronary revascularisation (FOURIER)</b>				
ODYSSEY OUTCOMES	903/9462 (9.5%)	1052/9462 (11.1%)	-	0.85 (0.78, 0.93)
FOURIER	-	1563/13780 (11.3%)	1344/13784 (9.8%)	0.85 (0.79, 0.92)
Alirocumab vs evolocumab				1.00 (0.89, 1.13)
<b>Time to fatal or non-fatal myocardial infarction<sup>a</sup></b>				
ODYSSEY OUTCOMES	646/9462 (6.8%)	756/9462 (8.0%)	-	0.85 (0.76, 0.94)
FOURIER	-	639/13780 (4.6%)	468/13784 (3.4%)	0.73 (0.65, 0.82)
Alirocumab vs evolocumab				1.16 (0.99, 1.36)
<b>Time to fatal or non-fatal ischaemic stroke (ODYSSEY OUTCOMES); or Time to stroke including ischaemic, haemorrhagic or unknown (FOURIER)</b>				
ODYSSEY OUTCOMES	111/9462 (1.2%)	152/9462 (1.6%)	-	0.73 (0.57, 0.93)
FOURIER	-	262/13780 (1.9%)	207/13784 (1.5%)	0.79 (0.66, 0.95)
Alirocumab vs evolocumab				0.97 (0.71, 1.33)
<b>Time to unstable angina requiring hospitalisation</b>				
ODYSSEY OUTCOMES	37/9462 (0.4%)	60/9462 (0.6%)	-	0.61 (0.41, 0.92)
FOURIER	-	239/13780 (1.7%)	236/13784 (1.7%)	0.99 (0.82, 1.18)
Alirocumab vs evolocumab				<b>0.62 (0.40, 0.96)</b>
<b>Time to ischaemia-driven coronary revascularisation (ODYSSEY OUTCOMES); or Time to coronary revascularisation (FOURIER)</b>				
ODYSSEY OUTCOMES	731/9462 (7.7%)	828/9462 (8.8%)	-	0.88 (0.79, 0.97)
FOURIER	-	965/13780 (7.0%)	759/13784 (5.5%)	0.78 (0.71, 0.86)
Alirocumab vs evolocumab				1.13 (0.98, 1.30)
<b>Time to cardiovascular death</b>				
ODYSSEY OUTCOMES	240/9462 (2.5%)	271/9462 (2.9%)	-	0.88 (0.74, 1.05)
FOURIER	-	240/13780 (1.7%)	251/13784 (1.8%)	1.05 (0.88, 1.25)
Alirocumab vs evolocumab				0.84 (0.65, 1.07)
<b>Time to death from any cause</b>				
ODYSSEY OUTCOMES	334/9462 (3.5%)	392/9462 (4.1%)	-	0.85 (0.73, 0.98)
FOURIER	-	426/13780 (3.1%)	444/13784 (3.2%)	1.04 (0.91, 1.19)
Alirocumab vs evolocumab				0.82 (0.67, 1.00)

Source: Table 2.6.8, p139 and Table 2.6.9, p140 of the resubmission

Abbreviations: CI, confidence interval; HR, hazard ratio

<sup>a</sup> The resubmission conducted alternative analyses for this outcome, claiming this outcome from the FOURIER was not clearly defined (all events or non-fatal events). The supplementary appendix to the Sabatine (2017) publication confirms that the outcome included non-fatal and fatal myocardial infarction events.

6.25 There were no statistically significant differences in cardiovascular events when comparing alirocumab with evolocumab using placebo as a common reference, except for unstable angina requiring hospitalisation with results in favour of alirocumab. However, these results are difficult to interpret due to major issues of exchangeability between the trials in terms of the inclusion criteria of the trials, the definitions of cardiovascular endpoints (particularly components contributing to composite endpoints), baseline cardiovascular risk, circumstances of use of treatments,

background lipid lowering therapies and follow-up duration. These differences are highlighted by the variability in the incidence of events occurring in the common reference arm for myocardial infarction, unstable angina and cardiovascular death.

- 6.26 The resubmission claimed that alirocumab was non-inferior in terms of efficacy compared with evolocumab based on the upper bound of the 95% confidence interval of the hazard ratio not exceeding 1.5 for the primary composite endpoint in the trials (HR 1.00, 95% CI 0.89, 1.13). The nominated non-inferiority margin was inadequately justified in the resubmission and did not appear reasonable given it exceeds the estimated difference for both treatments compared to placebo (approximately 15% for both interventions). This is also substantially higher than the clinically meaningful margins identified in the submission (5–6%)<sup>1</sup>, although they looked at LDL-c outcomes rather than hard outcomes such as MACE. The ESC considered this to be an overly generous NI margin, noted that it was not justified nor pre-specified, and therefore advised that the non-inferiority claim should be interpreted with caution.
- 6.27 The resubmission presented supportive analyses based on an indirect comparison of lipid outcomes with alirocumab versus evolocumab in he-FH populations (FH I, FH II, RUTHERFORD I, RUTHERFORD II) to address the applicability of the ODYSSEY OUTCOMES trial (predominantly non-familial patients) to the target PBS population with he-FH.
- 6.28 The inclusion/exclusion of trials for the indirect comparison was not adequately justified in the resubmission. The ESCAPE, HIGH FH and Stein 2012 trials of alirocumab in heterozygous familial populations included dosing regimens requested for reimbursement (alirocumab 150 mg fortnightly).
- 6.29 The robustness of meta-analysed results used in the indirect analyses for alirocumab was unclear given moderate heterogeneity between the FH I and II trials ( $I^2 = 54%$ ) which was not addressed in the resubmission. Additionally, the exchangeability of the alirocumab and evolocumab trials was also unclear given the varying trial designs and different patient characteristics, particularly baseline LDL.
- 6.30 The analyses presented in the resubmission did not directly address the comparative efficacy of the individual doses of alirocumab with evolocumab (recommended doses in the product information).
- 6.31 During the evaluation, alternative indirect analyses were conducted comparing the results of the available alirocumab trials versus evolocumab using placebo as the common comparator in familial hypercholesterolaemia populations (shown in table below). The analyses were conducted comparing the individual doses of alirocumab with evolocumab at matching dosing frequencies. Similar to the analyses presented in the resubmission, these analyses were limited by heterogeneity between the alirocumab trials and uncertain exchangeability between the evolocumab and

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<sup>1</sup>(Eriksson et al 2011, Saku et al 2011, Zhao and Peng 2017, see Table 2.4.14, p98 of the resubmission).

alirocumab trials.

- 6.32 The ESC noted that the submission identified three non-inferiority trials of statins (Eriksson et al., 2011, Saku et al., 2011, Zhao and Peng, 2017) that included percent change in LDL-c from baseline, and that the non-inferiority margins were between 5%–6%.

**Table 8: Indirect comparison of change in mean LDL levels with alirocumab and evolocumab in heterozygous familial hypercholesterolaemia populations using placebo as a common reference**

Comparison	Treatment difference, Mean (95% CI)
Alirocumab 75/150 mg fortnightly (FH I and II, Week 24, ITT) versus evolocumab 140 mg or 420 mg monthly (RUTHERFORD I and II, Week 12, ITT analysis)	3.16 (-2.52, 8.84)
Alirocumab 75 mg fortnightly (FH I and II, Week 12, no titration subgroup) versus evolocumab 140 mg fortnightly or 420 mg monthly (RUTHERFORD I and II, Week 12, ITT analysis)	■ (■, ■)
<b>Alirocumab 75 mg fortnightly versus evolocumab 140 mg fortnightly</b>	
Alirocumab 75 mg fortnightly (FH I and II, Week 12, ITT) versus evolocumab 140 mg fortnightly (RUTHERFORD II, Week 12, ITT)	<b>10.30 (3.25, 17.35)</b>
Alirocumab 75 mg fortnightly (FH I and II, Week 12, no titration subgroup) versus evolocumab 140 mg fortnightly (RUTHERFORD II, Week 12, ITT)	■ (■, ■)
Alirocumab 75 mg fortnightly (FH I and II, Week 24, no titration subgroup) versus evolocumab 140 mg fortnightly (RUTHERFORD II, Week 12, ITT)	■ (■, ■)
Alirocumab 75 mg fortnightly (FH I and II, Week 12, up-titration subgroup) versus evolocumab 140 mg fortnightly (RUTHERFORD II, Week 12, ITT)	■ (■, ■)
<b>Alirocumab 150 mg fortnightly versus evolocumab 140 mg fortnightly</b>	
Alirocumab 150 mg fortnightly (ESCAPE, HIGH FH, Stein 2012, Week 6/12/24, ITT) versus evolocumab 140 mg fortnightly (RUTHERFORD II, Week 12, ITT)	8.46 (-3.81, 20.73)
Alirocumab 150 mg fortnightly (FH I and II, Week 24, up-titration subgroup) versus evolocumab 140 mg fortnightly (RUTHERFORD II, Week 12, ITT)	■ (■, ■)
<b>Alirocumab 75/150 mg fortnightly versus evolocumab 140 mg fortnightly</b>	
Alirocumab 75/150 mg fortnightly (FH I and II, Week 12, ITT) versus evolocumab 140 mg fortnightly (RUTHERFORD II, Week 12, ITT)	4.18 (-4.44, 12.80)
<b>Alirocumab 300 mg 4-weekly (monthly) versus evolocumab 420 mg monthly</b>	
Alirocumab 300 mg 4-weekly (Stein 2012, Week 12, ITT) versus evolocumab 420 mg monthly (RUTHERFORD I and II, Week 12, ITT)	<b>27.09 (11.98, 42.20)</b>

Source: Table 2.7.8, p156 and Table 2.7.9, p157 of the resubmission; Table 2, p.4, and Table 3, p.6, FH I CSR; Table 10.6.1.1, p.169, Table 10.6.1.2, p.242, Table 10.6.2.1.16, p.264, and Table 10.6.1.16, p.265, FH II CSR; Ginsberg et al. (2016); Moriarty et al. (2016); Stein et al. (2012); Raal et al. (2012); Raal et al. (2015).

Abbreviations: CI, confidence interval; ITT, intention-to-treat; SE, standard error

*Italicised results were calculated during the evaluation*

*Note that a positive treatment difference indicates a smaller LDL reduction with alirocumab compared with evolocumab.*

- 6.33 Based on the indirect analyses, the resubmission claimed no statistically significant difference in relative LDL reduction associated with alirocumab compared with evolocumab. These results should be interpreted with caution as the analyses were based on a limited body of evidence (e.g. selected trials and subgroups of patients from FH I and FH II that did not require up-titration to achieve target LDL thresholds).
- 6.34 The alternative indirect analyses suggest that treatment with lower-dose alirocumab (75 mg fortnightly or 300 mg 4-weekly) was associated with statistically significantly lower reductions in LDL levels compared with evolocumab 140 mg fortnightly or 420 mg monthly. However, there was no statistically significant difference between lower-dose alirocumab and evolocumab in the subgroup of patients that did not require up-titration. There was no statistically significant difference between higher dose alirocumab treatment regimens (150 mg fortnightly, titration 75-150 mg fortnightly) and evolocumab.

- 6.35 The PSCR stated the titration protocol of the alirocumab trials used in the additional analyses only allowed up-titration to occur from Week 12; and as such, not all patients were optimally dosed at the timing of the Week 12 LDL-C measurement. The ESC noted that there was no statistically significant difference with evolocumab in the 75mg fortnightly dose for patients that did not require up-titration; however, the patient numbers in these subgroup analyses were small and, other than in one instance, the point estimates of the non-statistically significant differences consistently favoured evolocumab. The ESC also noted the confidence intervals were wide for both the analyses presented in the resubmission, using the data which pooled the doses of alirocumab, and the additional analyses from the evaluation. Based on the margins identified in the resubmission, non-inferiority would not be met.

### ***Comparative harms***

- 6.36 The most frequently reported adverse events associated with alirocumab were infections and infestations, musculoskeletal (myalgia, muscle spasms, musculoskeletal pain), general disorders and administration site conditions (fatigue, injection site reactions), and gastrointestinal disorders (diarrhoea, nausea, constipation).
- 6.37 In regards to adverse events of special interest, treatment with alirocumab was associated with a higher incidence of local injection site reactions.
- 6.38 An expanded assessment of harms identified important risks including hypersensitivity reactions and immunogenicity (i.e. development of anti-alirocumab antibodies). Important potential risks include cataract (in very low LDL levels) and neurocognitive disorders. No new safety signals were identified.
- 6.39 No new safety signals were identified in additional safety data from the OLE study of he-FH patients (up to 3.5 years of follow-up).
- 6.40 The PBAC has previously considered safety data from the FOURIER trial (and EBBINGHAUS sub-study of neurocognitive measures) and other evolocumab lipid trials in the July 2018 evolocumab submission.
- 6.41 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).
- 6.42 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. There was no statistically significant difference in neurocognitive measures between evolocumab and placebo for patients enrolled in the EBBINGHAUS sub-study.
- 6.43 There was a lack of data to adequately assess the comparative safety of alirocumab and evolocumab.

### **Benefits/harms**

- 6.44 A benefits/harms summary was not presented for alirocumab versus evolocumab due to the claim of non-inferiority.
- 6.45 On the basis of direct evidence presented in the resubmission, for every 1000 patients with recent ACS and hypercholesterolaemia (LDL-C  $\geq 1.81$  mmol/L) treated with alirocumab in comparison to placebo over a median duration of 2.8 years would result in:
- Approximately 2 fewer patients with a major adverse cardiovascular event, primarily driven by a difference in myocardial infarction
  - No apparent difference in adverse events
- 6.46 On the basis of direct evidence presented in the resubmission, for every 1000 patients with recent ACS, hypercholesterolaemia (LDL-C  $\geq 2.6$  mmol/L) and diabetes treated with alirocumab in comparison to placebo (median duration unreported, up to 4 years of follow-up) would result in:
- Approximately 7 fewer patients with a major adverse cardiovascular event, primarily driven by a difference in myocardial infarction
  - No apparent difference in adverse events

### **Clinical claim**

- 6.47 The resubmission described alirocumab as non-inferior in terms of efficacy and safety compared to evolocumab for the treatment of patients with he-FH with/without atherosclerotic cardiovascular disease and very high LDL levels. The evaluation considered the efficacy claim may not be adequately supported due to the limitations with the indirect analyses of the ODYSSEY OUTCOMES and FOURIER trials. The results were difficult to interpret due to major issues of exchangeability of composite cardiovascular endpoints, baseline risk, circumstances of use of treatments, background therapies, follow-up durations and the applicability of pre-dominantly non-familial trial populations to the PBS population with familial disease. Based on supportive indirect analyses of lipid trials, the efficacy claim may be reasonable for higher strengths of alirocumab (titration 75-150 mg fortnightly, 150 mg fortnightly) but is not adequately supported for lower strengths (75 mg fortnightly or 300 mg monthly). The ESC considered the non-inferiority of the higher strength may be reasonable, although it was only weakly supported given the confidence intervals were wide and non-inferiority margins may not be met. The ESC advised that equi-effective dosing should not be based on analyses which pool the doses of alirocumab, given the potential reduced effectiveness of the 75mg fortnightly dose. The distribution of patients in clinical practice that will or will not require up-titration is unknown, and thus the implication of flat pricing is that there may be some inflated pricing for at least several months (up to 24 weeks) for those patients not optimally dosed at 75mg fortnightly. The safety claim may be reasonable despite the lack of comparative data.

- 6.48 The resubmission described alirocumab as superior in terms of efficacy and non-inferior in terms of safety compared to placebo for the treatment of patients with previous ACS and diabetes who have elevated LDL levels. The efficacy claim may be reasonable based on the direct comparison of treatments in the ODYSSEY OUTCOMES trial (although alirocumab was not associated with a reduction in cardiovascular mortality). The safety claim was not reasonable given the higher incidence of local injection-site reactions associated with alirocumab. The ESC advised that the clinical trial data do not support the safety claim, despite no significant safety issues having been identified (higher injection site reactions and development of anti-alirocumab antibodies).
- 6.49 The PBAC considered the claim of non-inferior comparative effectiveness versus evolocumab was reasonable for the 150 mg fortnightly dose of alirocumab but was not adequately supported by the data for the 75 mg fortnightly or 300 mg monthly.
- 6.50 The PBAC considered that the claim of superior comparative effectiveness versus placebo was reasonable.
- 6.51 The PBAC considered that the claim of similar comparative safety was reasonable compared to evolocumab, though not supported in comparison to placebo.

### ***Economic analysis***

#### **Heterozygous Familial Hypercholesterolaemia (he-FH)**

- 6.52 The resubmission presented a cost-minimisation analysis for the comparison of alirocumab versus evolocumab for the he-FH indication.
- 6.53 The resubmission assumed that alirocumab 75 mg fortnightly or 300 mg every 4 weeks, with potential up-titration to 150 mg fortnightly is equivalent to evolocumab 140 mg fortnightly or 420 mg monthly. This was consistent with recommended doses in the product information for the treatment of patients with he-FH. The product information recommends alirocumab 75 mg fortnightly or 300 mg 4-weekly as starting doses, with optional up-titration to a maximum of 150 mg fortnightly whereas evolocumab is recommended as a fixed dose of either 140 mg fortnightly or 420 mg monthly only.
- 6.54 The evaluation considered the assumed equi-effective doses may not be reasonable given limitations with the indirect analyses of the key cardiovascular outcomes trials, and supportive analyses of lipid trials indicating no statistically significant difference between alirocumab and evolocumab using higher strengths of alirocumab but not for lower strengths. The PSCR disagreed and argued calculation of equi-effective doses unnecessary given the proposed flat pricing structure. However, the ESC noted the concerns around the non-inferiority claim based on lipid trial data that pooled the doses, with non-inferiority supported with up-titration from 75mg fortnightly to 150mg fortnightly by 24 weeks. The proportion of patients in clinical practice reaching optimal lipid control with 75mg fortnightly dosing is unknown. An average dose at steady state of alirocumab across the lipid trials was not used to determine equi-effective doses. The ESC considered the higher dose of alirocumab, i.e. 150 mg

fortnightly, may be used as an equi-effective dose to evolocumab 140 mg fortnightly or 420 mg monthly. To avoid the risk of less effective therapy being priced the same as evolocumab, the PBAC agreed with the ESC and advised that pricing of the lower dose of alirocumab will be determined by the Department according to usual methods.

- 6.55 The pre-PBAC response argued that the PBAC Guidelines recommend calculating equi-effective doses at steady state, i.e. the average dose after dose titrations are complete, which would include a proportion of patients on 75 mg and a proportion on 150 mg.
- 6.56 The sponsor did not conduct a cost-minimisation analysis, as the effective price of evolocumab was unknown. The PSCR stated that indication specific pricing was being sought, based on a weight of 19% for the he-FH population (CMA to evolocumab) and 81% for the non-FH population.

**Non-Familial Hypercholesterolaemia (non-FH)**

- 6.57 The resubmission presented a stepped economic evaluation of alirocumab 75 mg (up-titratable to 150 mg) fortnightly for the treatment of patients with non-FH with prior ACS, diabetes and LDL  $\geq 2.6$  mmol/L as an add-on therapy to statins.
- 6.58 No economic evaluation was presented for alirocumab when used in addition to ezetimibe in statin-intolerant patients, noting the proposed indication includes patients with statin intolerance as well as those experiencing inadequate control with statins.
- 6.59 The economic evaluation was based on mean TC:HDL ratios transformed to cardiovascular outcomes based on the ODYSSEY OUTCOMES trial subgroup and other modelled variables.

**Table 9: Summary of model structure and rationale**

Component	Description
Type of analysis	Cost-utility analysis
Methods used to generate results	Markov cohort model (with half-cycle correction)
Time horizon	41 years
Cycle length	1 year
Discounting	5% for costs and outcomes applied annually
Health states	Four health states: pre-recurrent CHD, recurrent CHD (myocardial infarction or angina), CHD death and non-CHD death
Outcomes	% reduction in TC:HDL, life years gained, quality-adjusted life years
Transition probabilities	<p>Transition probabilities were derived from the Framingham risk equation for predicting subsequent CHD events (D'Agostino 2000) using TC:HDL ratios from the ODYSSEY OUTCOMES subgroup with diabetes and LDL <math>\geq</math>2.6 mmol/L for Years 1-4 and assumed values from Years 5-40.</p> <p>The probability of a composite CHD event was adjusted using cardiovascular risk multipliers to match the cumulative incidence of CHD events (MACE without stroke) in the trial for Years 1-4 and assumed from Years 5-40.</p> <p>The composite event probability was distributed to an individual probability for CHD death using adjustments to match the cumulative CHD deaths (time to coronary death) in the trial for Years 1-4 and assumed from Years 5-40 using the distribution of fatal vs non-fatal events from the MACE without stroke composite endpoint.</p> <p>The probability of non-fatal events over the model lifetime was assumed to be the remaining probability (1 minus probability of CHD death) and distributed to individual probabilities of MI and angina using the relative distribution of non-fatal events from the MACE without stroke endpoint.</p> <p>The probability of non-CHD death was derived from ABS life tables adjusted for the proportion of deaths due to CHD.</p>
Software package	Excel 2010

Source: Table 3.1.1, p182 of the resubmission

Abbreviations: CHD, coronary heart disease; MACE, major adverse cardiovascular events; TC:HDL, total cholesterol to high density lipoprotein ratio

Note: MACE without stroke was based on a composite endpoint of time to coronary death, fatal or non-fatal myocardial infarction or unstable angina requiring hospitalisation

6.60 All patients start in pre-recurrent CHD health state (baseline health state). 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 the acute costs of each event. There were no ongoing chronic costs due to events. Once a patient has an event, the same health state utility is applied regardless of multiple events occurring. The model structure does not allow for appropriate implementation of treatment discontinuations, with persistence estimates applied to drug costs only without change in treatment effect.

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

**Table 10: Key drivers of the model**

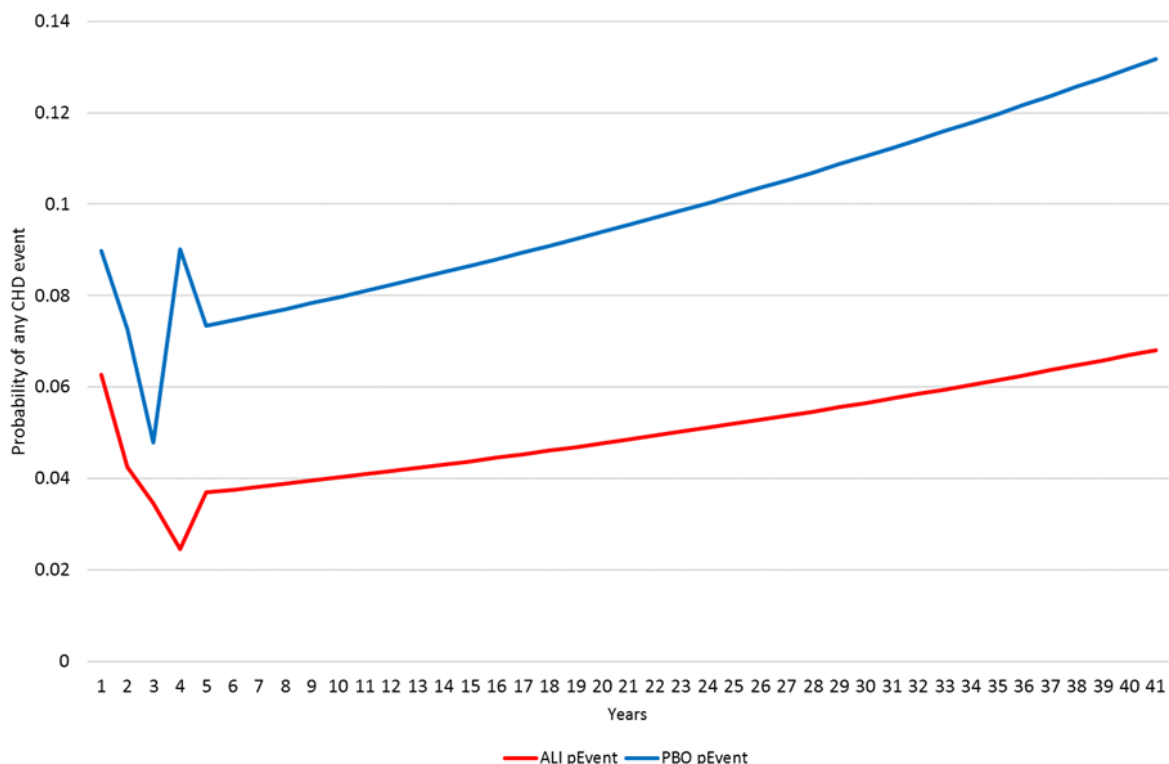
Description	Method/Value	Impact
Modelled patient population	<p>The modelled population was based on the subgroup of patients with recent ACS, diabetes and LDL <math>\geq 2.6</math> mmol/L that was not directly applicable to the target PBS population with a history of ACS (includes stable patients).</p> <p>The modelled population has a higher baseline risk than the ODYSSEY OUTCOMES overall trial population, however, the model also assumed a higher relative treatment effect with alirocumab that has not been demonstrated. The ESC noted the hazard ratios and CIs provided in the PSCR (p3) showed overlap with the ITT population indicating that there is still some uncertainty regarding the treatment effect in this subgroup. The use of efficacy results from this subgroup is likely to overestimate treatment effects associated with alirocumab in the economic model. Due to model structure, changes in baseline risk and treatment effect between the model and trial populations could not be assessed.</p>	High, favours alirocumab
Transition probabilities	<p>The transition probabilities were derived using Framingham risk equations for subsequent CHD events (D'Agostino 2000). There were multiple concerns noted in the previous commentary in regard to the inappropriate use of Framingham risk equations to derive transition probabilities in the model including the application of individual risk calculators to predict population estimates, synthesis of short-term risk models to predict long-term risk and the generalisability of the risk equations that did not include all risk factors associated with cardiovascular disease (e.g. non-US settings, various ethnic populations, family history, obesity). These issues were inadequately addressed in the resubmission.</p> <p>The resubmission acknowledged differences in the incidence of events occurring in the trial versus predicted events using the Framingham equations that were dependent on change in TC:HDL ratio, and therefore used cardiovascular risk multipliers to increase the risk of CHD events predicted in the model to match events occurring in the trial. The use of Framingham risk equations to model CHD events was inappropriate given the mismatch in predicted outcomes compared with the trial results. The ESC considered the use of the Framingham model was not preferred when CV outcomes data are available from the clinical trials. The resubmission acknowledged that the underlying cardiovascular risk of the trial population with a recent ACS is typically higher in the short-term, which is not captured by the Framingham equations.</p> <p>The distribution of individual events was synthesized using data from the individual outcome of time to coronary death and components of fatal and non-fatal events from the MACE without stroke composite endpoint. The distribution of the probability of CHD death derived from the individual outcome is likely to overestimate the risk of CHD death when applied to the probability of any CHD event that was based on the MACE without stroke composite endpoint (first event captured only).</p> <p>Extrapolated transition probabilities from Years 5-41 of the model were assumed. The resubmission did not provide adequate validation of these estimates.</p>	High, favours alirocumab
Treatment effect on coronary death	<p>The modelled approach using the Framingham risk equations, cardiovascular risk multipliers and adjustments to event distributions resulted in a substantial reduction in mortality associated with alirocumab compared with placebo.</p> <p>In contrast, the ODYSSEY OUTCOMES trial evidence suggests no treatment effect on cardiovascular mortality that was consistent with data from the FOURIER trial for evolocumab. The PBAC previously considered the incorporation of a mortality time lag as a potential method to address this uncertainty when raised with the evolocumab FOURIER trial (para 6.33 and 7.6, evolocumab PSD July 2018). The PSCR (p4) argued the model implicitly incorporated a mortality lag as visual inspection of the MACE and the CV mortality curves of the trial show the MACE curves separating earlier than the CV mortality curves. The ESC considered the extent of separation of the curves for CV mortality remained optimistic and the extrapolation using Framingham overestimated the magnitude of this difference.</p>	High, favours alirocumab

Source: compiled during the evaluation

Abbreviation: ACS, acute coronary syndrome

6.62 The impact of deriving transition probabilities using Framingham risk equations, cardiovascular risk multipliers and adjusted event distributions over time was explored during the evaluation. Figure 2 illustrates the transition probabilities of any CHD event (myocardial infarction, angina or CHD death) over time.

**Figure 2: Transition probabilities of any CHD event in the economic model**



Source: constructed during the evaluation using 'ALI\_model\_Oct18' Excel workbook

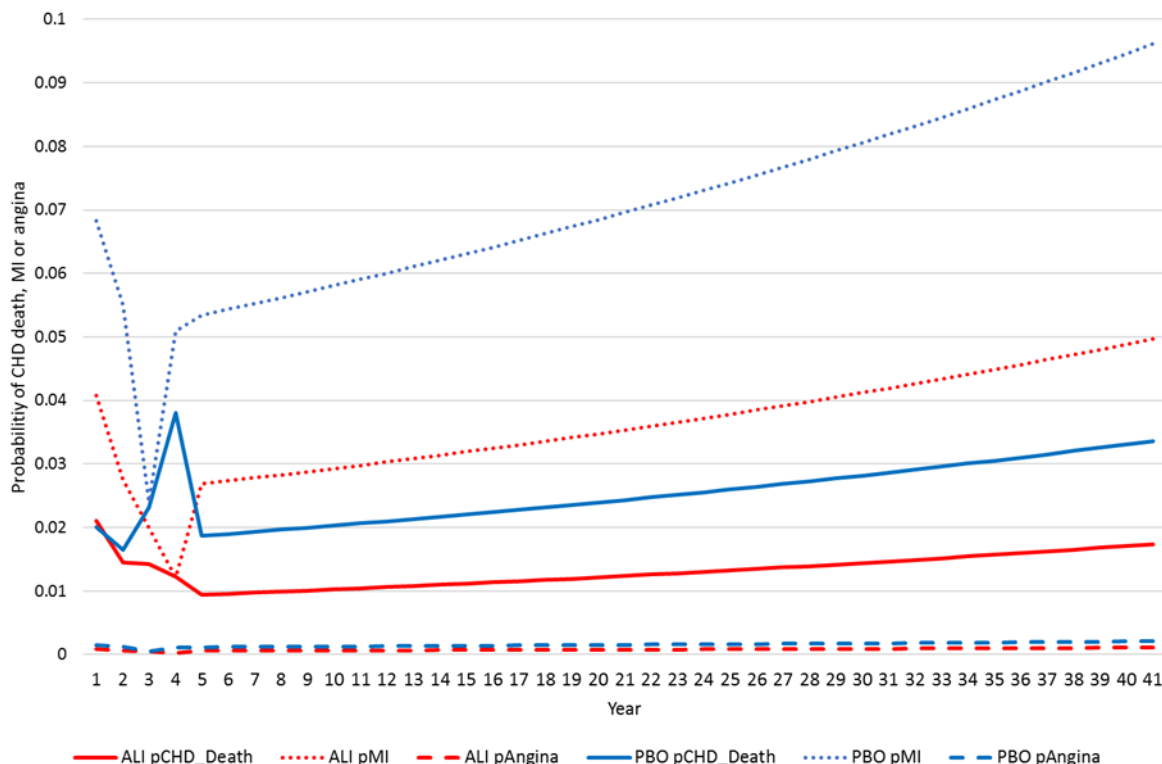
Abbreviations: ALI, alirocumab; CHD, coronary heart disease; pEvent, probability of any CHD event; PBO, placebo

6.63 The graph shows a decreasing risk of CHD events in both arms in the first 3 years of the model followed by divergence between arms in years 3-4 with a sharp increase for placebo and continued decrease in risk for alirocumab. Relatively small patient numbers limited trial data used to inform the estimates at Year 4.

6.64 From Year 5 onwards, a difference in the risk of CHD events that gradually widened over the model lifetime was assumed. This assumption had a large impact and was substantially in favour of alirocumab.

6.65 Figure 3 presents the individual transition probabilities of CHD death, myocardial infarction and angina in the model.

Figure 3: Transition probabilities of CHD death, myocardial infarction or angina in the model



Source: constructed during the evaluation using 'ALI\_model\_Oct18' Excel workbook  
 Abbreviations: ALI, alirocumab; CHD, coronary heart disease; PBO, placebo

- 6.66 The graph shows a decreasing risk of myocardial infarction trending towards convergence between treatment arms by Year 3, followed by substantial divergence at Year 4. At Year 5, the risk of myocardial infarction in the alirocumab sharply increases and a relative treatment effect versus placebo is then maintained for the rest of the model duration.
- 6.67 There was no difference in the risk of CHD death at Year 1 of the model, with divergence starting at Year 2 and a peak difference at Year 4 in the model (largely due to a temporary spike in the placebo arm). At Year 5, the risk of CHD death in the placebo arm decreases sharply and a relative treatment effect in favour of alirocumab is maintained until the end of the model.
- 6.68 Overall, the modelled CHD risks did not appear to be clinically plausible and lacked face validity.
- 6.69 The results of the modelled economic evaluation are summarised below.

Table 11: Results of the stepped economic evaluation

Step and component	Alirocumab	Placebo	Increment
<b>Step 1: Trial-based incidence of CHD event (based on time to first non-fatal or fatal MI, angina or CHD death) from ITT population with fixed drug costs up to 4 years.</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
CHD events	0.0860	0.0995	-0.0134
Incremental cost per CHD event avoided			Add \$ [REDACTED]
<b>Step 2: Trial-based incidence of CHD event (based on time to first non-fatal or fatal MI, angina or CHD death) from subgroup with LDL <math>\geq</math>2.6 mmol/L with fixed drug costs up to 4 years.</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
CHD events	0.1031	0.1346	-0.0316
Incremental cost per CHD event avoided			\$ [REDACTED]
<b>Step 3: Trial-based incidence of CHD event (based on time to first non-fatal or fatal MI, angina or CHD death) from subgroup with diabetes and LDL <math>\geq</math>2.6 mmol/L with fixed drug costs up to 4 years.</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
CHD events	0.1261	0.1895	-0.0633
Incremental cost per CHD event avoided			\$ [REDACTED]
<b>Step 4: Transform TC:HDL ratio and patient characteristics from subgroup with diabetes and LDL <math>\geq</math>2.6 mmol/L to CHD events (via Framingham equation) and distribute to non-fatal MI, angina or CHD death using event distribution from post-hoc subgroup analysis with fixed drug costs up to 4 years.</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
CHD events	0.1537	0.1990	-0.0458
Incremental cost per CHD event avoided			\$ [REDACTED]
<b>Step 5a: Adjust probability of CHD events from Framingham equation to match incidence and distribution of events in the subgroup from the trial with fixed drug costs up to 4 years.</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
CHD events	0.1594	0.2880	-0.1291
Incremental cost per CHD event avoided			\$ [REDACTED]
<b>Step 5b: Use modelled drug costs up to 4 years.</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
CHD events	0.1594	0.2880	-0.1291
Incremental cost per CHD event avoided			\$ [REDACTED]
<b>Step 6: Include modelled CHD event costs up to 4 years.</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
CHD events	0.1594	0.2880	-0.1291
Incremental cost per CHD event avoided			\$ [REDACTED]
<b>Step 7: Transform outcomes to life years gained.</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYs	3.5664	3.5436	0.0228
Incremental cost per LY gained			\$ [REDACTED]
<b>Step 8: Extrapolate health outcomes, modelled drug and CHD event costs to 41 years.</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYs	12.7937	11.6284	1.1653
Incremental cost per LY gained			\$ [REDACTED]
<b>Step 9: Transform outcomes to quality adjusted life years using utility values for each health state.</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	10.4251	9.3797	1.0454
Incremental cost per QALY gained (base case)			\$ [REDACTED]

Source: Table 3.8.2, p212 of the resubmission

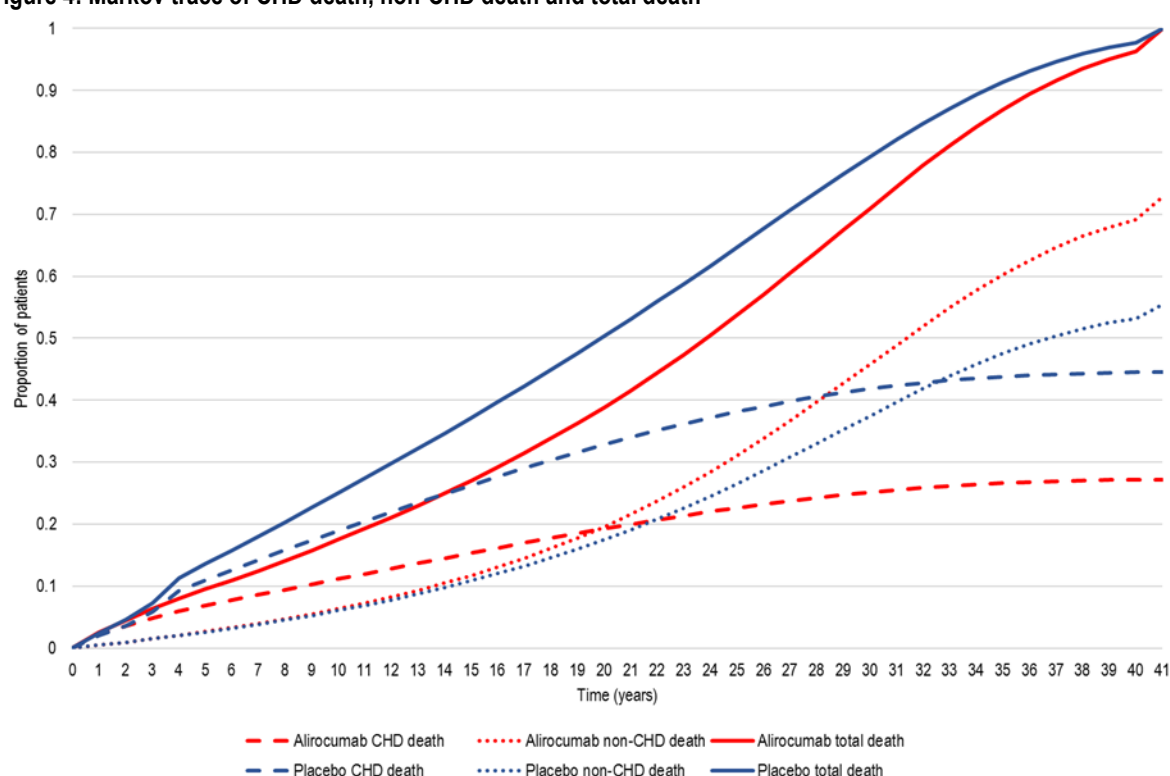
Abbreviations: CHD, coronary heart disease; HDL, high density lipoprotein; LYs, life years; MI, myocardial infarction; TC, total cholesterol; QALYs, quality-adjusted life years

Note: An alternative stepped economic analysis was conducted during the evaluation by rearranging the steps used in the resubmission and adding additional steps to explore the impact of using modelled drug costs and extrapolation

6.70 The extrapolation of the modelled time horizon to 41 years and the use of higher risk subgroups based on LDL threshold and the combination of diabetes and elevated LDL had large impacts on the economic evaluation. Earlier steps in the analysis (steps 1-5a) were conducted assuming fixed drug costs which are expected to vary by changing populations due to event distributions (e.g. deaths had no impact on drug costs). The results from step 3 should be interpreted with caution, as the confidence intervals are relatively wide for the post-hoc subgroup data that is used to suggest greater relative benefit with alirocumab treatment.

6.71 During the evaluation, Markov traces were constructed to illustrate the cumulative incidence of mortality outcomes over the duration of the model.

**Figure 4: Markov trace of CHD death, non-CHD death and total death**



Source: constructed during the evaluation from the 'ALI-model\_Oct18' Excel workbook of the resubmission  
Abbreviations: CHD, coronary heart disease

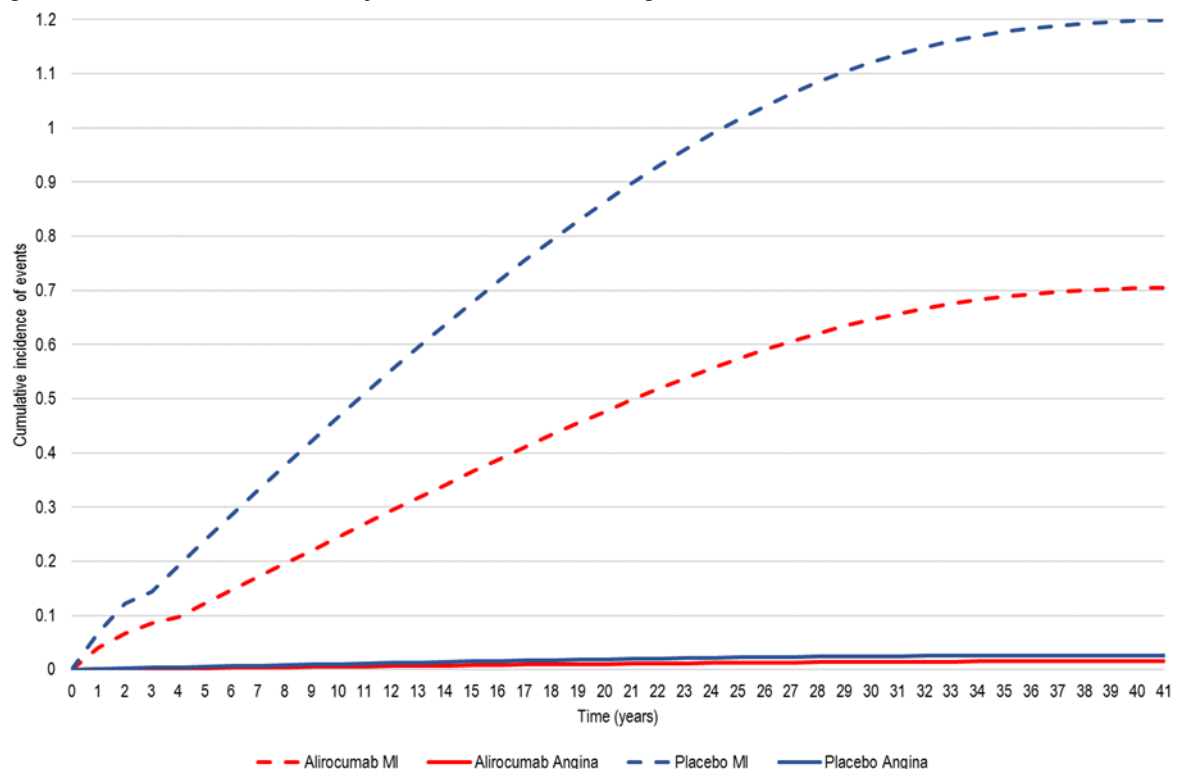
6.72 The model generated substantial reductions in coronary death for alirocumab versus placebo with the curves starting to diverge between Year 2 and 3. This was inconsistent with evidence from the ODYSSEY OUTCOMES trial that showed no apparent difference in coronary death between alirocumab and placebo.

6.73 The PBAC previously considered the incorporation of a mortality time lag as a potential method to address this uncertainty when raised with the evolocumab FOURIER trial (para 6.33 and 7.6, evolocumab PSD July 2018). The ESC noted a 2019 paper by Szarek

M et al<sup>2</sup>, may provide some supportive analysis that a total events analysis (as opposed to first event only) shows that the occurrence of nonfatal events increases the risk of subsequent death and hence the mortality benefit may accrue as the person experiences additional events over time. Given the timing of the publication, this paper was not included in the evaluation.

6.74 The cumulative incidence of myocardial infarction and angina over the duration of the model is presented below.

Figure 5: Cumulative incidence of myocardial infarction and angina



Source: constructed during the evaluation from the 'ALI-model\_Oct18' Excel workbook of the resubmission  
Abbreviation: MI, myocardial infarction

6.75 The traces show alirocumab was associated with substantial reductions in myocardial infarction and almost no difference in angina events compared with placebo. The resubmission did not attempt to validate the modelled estimates with data from the ODYSSEY OUTCOMES trial or other external sources.

6.76 The results of key sensitivity analyses are summarised below.

<sup>2</sup> Szarek M, White HD, Schwartz GG, Alings M, Bhatt DL, Bittner VA, Chiang CE, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Kimura T, Kiss RG, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Roe MT, Tricoci P, Xavier D, Zeiher AM, Steg PG. (2019) 'Alirocumab Reduces Total Nonfatal Cardiovascular and Fatal Events: The ODYSSEY OUTCOMES Trial'. *Journal of the American College of Cardiology*. 73(4):387-396.

Table 12: Results of sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
Base case	\$ [REDACTED]	1.0454	\$ [REDACTED]
<b>Model time horizon (base case: 41 years)</b>			
4 years	\$ [REDACTED]	0.0287	\$ [REDACTED]
10 years	\$ [REDACTED]	0.2548	\$ [REDACTED]
20 years	\$ [REDACTED]	0.6917	\$ [REDACTED]
30 years	\$ [REDACTED]	0.9700	\$ [REDACTED]
<b>Cardiovascular risk multipliers and adjusted event distribution (base case: calibration of Framingham risk equations and adjustments to individual event probabilities to match trial-based incidence; variable for Year 1-4 and fixed from Year 5+)</b>			
No cardiovascular risk multipliers and fixed individual event distribution (CHD death, 25.5%; MI, 72.9%; angina, 1.6%)	\$ [REDACTED]	0.3480	\$ [REDACTED]
<b>Years 5 to 41: Cardiovascular risk multiplier applied to Framingham risk equations (base case: alirocumab, 0.8253; placebo, 1.3663)</b>			
No multiplier (alirocumab, 1; placebo, 1)	\$ [REDACTED]	0.5381	\$ [REDACTED]
<b>Years 5 to 41: Distribution of CHD events that are fatal (base case: 25.5% in both arms)</b>			
Both arms 20%	\$ [REDACTED]	0.9429	\$ [REDACTED]
Both arms 30%	\$ [REDACTED]	1.1208	\$ [REDACTED]
<b>Utility value of pre-recurrent CHD health state (base case: 0.8300)</b>			
0.7800	\$ [REDACTED]	0.9871	\$ [REDACTED]
0.8800	\$ [REDACTED]	1.1036	\$ [REDACTED]
<b>Utility value of recurrent CHD health state (base case: 0.7674)</b>			
0.8300	\$ [REDACTED]	0.9672	\$ [REDACTED]
0.7048	\$ [REDACTED]	1.1235	\$ [REDACTED]
<b>CHD event costs (base case: MI \$ [REDACTED]; angina \$ [REDACTED]; CHD death \$ [REDACTED])</b>			
No event costs (\$0)	\$ [REDACTED]	1.0454	\$ [REDACTED]
All costs doubled (MI \$ [REDACTED]; angina \$ [REDACTED]; CHD death \$ [REDACTED])	\$ [REDACTED]	1.0454	\$ [REDACTED]
All costs halved (MI \$ [REDACTED]; angina \$ [REDACTED]; CHD death \$ [REDACTED])	\$ [REDACTED]	1.0454	\$ [REDACTED]

Source: Table 3.9.1, p216 of the resubmission  
Abbreviations: CHD, coronary heart disease

The redacted table shows ICERs in the range of \$45,000/QALY to more than \$200,000/QALY.

- 6.77 The model is most sensitive to the model time horizon, and the combination of cardiovascular risk multipliers and adjustments to the distribution of CHD events.
- 6.78 The ESC considered that the modelled economic analysis should have included the additional patient subgroup from the proposed indication that were statin intolerant.
- 6.79 The impact of varying treatment effects could not be reliably investigated with sensitivity analyses due to the structure of the economic model. The underlying cardiovascular risk of the modelled population and relative changes due to treatment effect were interdependent and could not be analysed separately. For example, predicted CHD deaths were estimated using a combination of absolute TC:HDL ratios and selected patient characteristics transformed using Framingham risk equations, cardiovascular risk multipliers to match trial-based incidence of any CHD event and adjustments to the distribution of events to match trial-based incidence of CHD deaths. The ESC considered this to be an inappropriate use of Framingham risk equations, which have the potential to overestimate effects in the long-term. The ESC

considered these equations are not preferred when CV outcomes data are available from the clinical trials.

**Drug cost/patient/year**

- 6.80 The estimated drug cost for alirocumab per patient per year for the non-FH population was \$ [REDACTED] (based on 13.04 scripts using the effective DPMQ \$ [REDACTED] for both the 75 mg fortnightly, 300 mg every 4 weeks and the 150 mg fortnightly injections).
- 6.81 The estimated drug cost for ezetimibe per patient per year was \$523.07, based on 12.17 scripts (30 days of therapy per script) using the DPMQ \$42.98.

**Estimated PBS usage & financial implications**

- 6.82 The resubmission was considered by DUSC. The resubmission took an epidemiological approach, and estimated use and financial implications for the he-FH patients with/without atherosclerotic disease and very high LDL levels and patients with non-FH with prior ACS, diabetes and elevated LDL levels separately, using different sources and assumptions for each.
- 6.83 Key changes to the budget impact estimates included a reduction in the proposed effective price for alirocumab, revised estimates for the he-FH population with/without atherosclerotic disease and very high LDL levels (revised restriction to align with current PBS listing for evolocumab) and the inclusion of estimates for the non-FH indication.
- 6.84 The table below presents the estimated utilisation and cost to the PBS of alirocumab for the familial hypercholesterolaemia population. The net cost to the PBS for the he-FH indication for alirocumab (DPMQ less patient co-payment) was less than \$10 million (published) and less than \$10 million (effective) in Year 6 of listing, with a cumulative total cost of \$30 to \$60 million (published) and \$20 to \$30 million (effective) in the first 6 years.

**Table 13: Estimated net cost of alirocumab to the PBS: Heterozygous familial hypercholesterolaemia (Effective price)**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Australian adult (18+) pop'n						
Prevalent population (0.28%)						
<b>Primary prevention (60% of all familial patients)</b>						
Without ASCVD						
Diagnosed (16% to 31%)						
LDL ≥ 5 mmol/L (5.4%)						
Uptake	%	%	%	%	%	%
Total patients						
<b>Secondary prevention (40% of all familial patients)</b>						
With ASCVD (100% diagnosed)						
LDL ≥ 3.3 mmol/L (28%)						
Uptake	%	%	%	%	%	%
Total patients						
<b>Estimated scripts and costs (10.43 scripts/patient/year)</b>						
Treated patients						
75 mg/mL scripts (70%)						
150 mg/mL scripts (30%)						
Total cost <sup>a</sup>	\$	\$	\$	\$	\$	\$
Net cost to PBS less copay	\$	\$	\$	\$	\$	\$

<sup>a</sup> Note: There was a flat pricing structure proposed in the resubmission for all dose strengths of alirocumab.

Source: ALI\_Section 4\_BudgetImpact.xlsx

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL, low density lipoprotein

*Italicised estimates were calculated during the evaluation by adjusting the uptake rates for alirocumab for secondary prevention to be the same as uptake rates assumed for primary prevention*

6.85 DUSC considered the estimates presented in the submission for he-FH patients with/without atherosclerotic disease and very high LDL levels to be underestimated. The main issues are:

- The number of treated he-FH patients was underestimated, due predominantly to an underestimate of the number of people with qualifying LDL levels and underestimated uptake rates in both primary and secondary he-FH.
- There is likely to be a substantial pool of patients who are not achieving target LDL levels with existing therapies but who would not be eligible for PBS-subsidised treatment with alirocumab. There is a high risk of use outside of the requested restriction for this population.

6.86 The table below presents the estimated utilisation and cost to the PBS of alirocumab for the non-FH population with prior ACS, diabetes and elevated LDL levels.

**Table 14: Estimated net cost of alirocumab to the PBS/RPBS: Non-familial hypercholesterolaemia (Effective price)**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Australian adult population						
ACS prevalence (3.6-4.0%)						
ACS and diabetes (27%)						
Ezetimibe use (19.1% - 38.3%)						
LDL ≥ 2.6 mmol/L (27.5%)						
Estimated uptake	%	%	%	%	%	%
<b>Total patients</b>						
75 mg/mL scripts (70%) <sup>a</sup>						
150 mg/mL scripts (30%) <sup>a</sup>						
Total scripts						
Total cost <sup>b</sup>	\$	\$	\$	\$	\$	\$
Net cost to PBS less co-pay	\$	\$	\$	\$	\$	\$

<sup>a</sup> Resubmission assumed 10.43 scripts/patient/year

<sup>b</sup> There was a flat pricing structure proposed in the resubmission for all dose strengths of alirocumab.

Source: ALI\_Section 4\_BudgetImpact.xlsx

Abbreviations: ACS, acute coronary syndrome; LDL, low-density lipoprotein

6.87 The net cost to the PBS for the non-FH indication for alirocumab (DPMQ less patient co-payment) was estimated at up to \$30 to \$60 million (published) and \$30 \$60 million (effective) in Year 6 of listing, a cumulative total of more than \$100 million (published) and more than \$100 million (effective) in the first 6 years.

6.88 DUSC considered the estimates presented for patients with non-FH with prior ACS, diabetes and elevated LDL levels to be uncertain but reasonable overall if the hospitalisation requirement is strictly applied. The main issues are:

- The survey data used to estimate the proportion of people with ACS relied on self-report and may not have captured the same patients as would be eligible under the narrow definition (hospitalisation) in the requested restriction.
- The proportion of patients with ACS and diabetes (27%) was applied to the ACS prevalent population in Australia. However, the patient numbers would differ if the proportion was applied to the prevalent diabetes population.
- The estimated proportion of non-familial patients taking ezetimibe who qualified for alirocumab based on LDL thresholds was derived from the clinical trial and might not be applicable to the PBS population.
- There may be potential for use outside the restriction in other high-risk populations who are not achieving target LDL levels with existing therapies.
- ACS was not well defined in the requested restriction and may be open to interpretation by prescribers.

6.89 The estimated use and total costs of listing alirocumab for both the familial and non-FH populations are summarised in the table below. The estimated cost of the overlapping population was calculated during the evaluation based on half of the alirocumab uptake for secondary prevention in he-FH patients (3.5% to 10.5% over 6 years).

**Table 15: Estimated cost to the PBS of alirocumab in the first six years of listing (effective price)**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
HeFH	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
ACS + diabetes	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Overlapping population	-\$ [REDACTED]	-	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
<b>Net cost to the PBS less copay</b>	<b>\$ [REDACTED]</b>	<b>\$ [REDACTED]</b>	<b>\$ [REDACTED]</b>	<b>\$ [REDACTED]</b>	<b>\$ [REDACTED]</b>	<b>\$ [REDACTED]</b>

<sup>a</sup> Note: There was a flat pricing structure proposed in the resubmission for all dose strengths of alirocumab.

Source: ALI\_Section 4\_BudgetImpact.xlsx

Abbreviations: ACS, acute coronary syndrome

*Italicised estimates were calculated during the evaluation*

- 6.90 The total cost to the PBS for listing alirocumab (DPMQ less patient co-payment) was estimated at less than \$10 million (published) and less than \$10 million (effective) in Year 1 of listing, increasing to \$30 to \$60 million (published) and \$30 to \$60 million (effective) in Year 6, a total of more than \$100 million (published) and more than \$100 million (effective) in the first 6 years of listing.
- 6.91 The resubmission did not provide any justification for the extent of the assumed overlap in patient populations between the two requested indications. Increasing or decreasing the proportion of patients fitting both indications (secondary familial hypercholesterolaemia as well as ACS and diabetes), will affect overall utilisation estimates.

### **Quality Use of Medicines**

- 6.92 The resubmission detailed the sponsor’s plans to address quality use of medicines issues, particularly around the method of administration (injection) that may not be familiar for some health professionals managing hypercholesterolaemia in Australia.
- 6.93 The sponsor stated they have a Risk Management Plan approved by the TGA, as well as plans for specific training and materials for health care professionals and patients on identifying appropriate patients, correct administration, prevention of medication errors, appropriate storage and handling and pharmacovigilance.
- 6.94 The resubmission did not adequately consider the prevention of medication errors due to the range of dosing regimens available to patients. There may be potential for confusion resulting from the starting doses recommended in the alirocumab product information: 300 mg once monthly and 75 mg fortnightly. The 300 mg once monthly dose and 150 mg maximum fortnightly dose are not equivalent. There may also be confusion related to the need to up-titrate alirocumab dosing in some patients who fail to achieve the target levels with the starting dose (unlike evolocumab, in which up-titration is not required).
- 6.95 The DUSC considered the resubmission did not adequately consider the prevention of medication errors due to the range of dosing regimens available to patients. The initial restriction is Authority Required – Written, and this will likely limit the initial prescribing of alirocumab to specialists. However, the continuing restriction is Authority Required – Telephone, and general practitioners (GPs) will likely be

responsible for the ongoing management of the patient. The different starting doses may cause confusion for GPs, and this may present a QUM issue for ongoing therapy.

### **Financial Management – Risk Sharing Arrangements**

- 6.96 The resubmission stated that the sponsor was willing to undertake a risk sharing arrangement, but did not provide any details regarding the arrangement.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended an Authority Required listing of alirocumab for the treatment of patients with heterozygous familial hypercholesterolaemia (he-FH) with high cardiovascular risk (patients with atherosclerotic disease and/or very high LDL levels) on a cost-minimisation basis to evolocumab. The PBAC did not recommend the listing of alirocumab for patients with non-familial hypercholesterolaemia (non-FH) with acute coronary syndrome (ACS) and diabetes based on an inadequately defined high-risk patient population, and a high and uncertain incremental cost-effectiveness ratio (ICER).

### **Heterozygous familial hypercholesterolaemia (he-FH)**

- 7.2 The PBAC recommended the listing of alirocumab for he-FH patients with the same restriction wording as evolocumab for this indication. The exception is an additional treatment criterion to highlight that treatment must commence on a 75 mg fortnightly, or 300 mg monthly, dose and to indicate that there should be no concomitant use with evolocumab.
- 7.3 The PBAC noted the recommended starting dose in the product information is either 75 mg fortnightly or 300 mg every 4 weeks, with the potential to up-titrate to a maximum dose of 150 mg fortnightly. Under the proposed listing, it is possible to administer the starting dose using either preparation (i.e. the 75 mg or 150 mg). Based on this, the PBAC advised that the initial restriction for alirocumab should be an Authority Required (Written) for the 75 mg fortnightly dose and the 150 mg dose (which could be used as 300 mg monthly). The maximum quantity for each strength would be 1 with 5 repeats. The PBAC also advised that the continuing restriction would be a Authority Required (Telephone) and would include both the 75 mg and the 150 mg fortnightly dose, to be individually determined depending on the patient's assessment of response.
- 7.4 The PBAC considered the clinical need for another PCSK9 inhibitor in this setting was not high, but noted an additional effective therapy for patients with FH at high risk of cardiovascular disease would provide an option for patients not responding to treatment with the already PBS-listed evolocumab.
- 7.5 The PBAC considered evolocumab, the nominated main comparator in patients with he-FH, to be appropriate.

- 7.6 The PBAC noted the key clinical trial evidence supporting the he-FH listing included an indirect comparison of alirocumab and evolocumab using cardiovascular outcomes data from the ODYSSEY OUTCOMES and FOURIER trials. The PBAC noted this ITC was previously requested by the Committee in November 2017. This indirect comparison was considered informative, although notably, there were exchangeability issues between the trials and the populations in both trials were not he-FH patients. There is no established non-inferiority margin for the MACE outcomes used in the ITC but the PBAC considered the hazard ratio (HR) of 1.00 (95% CI, 0.89-1.13) for the primary composite endpoint supported similar outcomes across the trials given the upper CI was within the estimated difference for both treatments compared to placebo (approximately 15% for both interventions). Non-inferiority based on the CV outcomes for he-FH was not definitive given the limitations with the indirect analyses of the ODYSSEY OUTCOMES and FOURIER trials.
- 7.7 The PBAC noted the supportive indirect analyses of lipid outcomes trials (FH I, FH II, RUTHERFORD I, RUTHERFORD II), presented in Section 6 provided a basis for establishing comparative effectiveness of alirocumab with evolocumab in the he-FH population. The PBAC considered the alternative indirect analyses conducted during the evaluation, including those with the additional trials (ESCAPE, HIGH FH and Stein 2012) were also informative.
- 7.8 The PBAC noted the submission requested consideration of the pooled outcomes of the 75 mg and 150 mg fortnightly doses in the lipid outcomes analyses. The PBAC noted there was an approximately █% difference in LDL reduction observed in subgroup analyses of patients receiving alirocumab who were up-titrated compared to those with no titration, and that the 75 mg fortnightly dose during initial treatment phases, up to 24 weeks, may result in reduced effectiveness when compared to the higher strengths of alirocumab. The PBAC was also concerned about the robustness of the non-inferiority claim given the wide confidence intervals and point estimates favouring evolocumab. The PBAC considered alirocumab was less efficacious at the lower strength (75 mg fortnightly) but the uncertainty in the ITC did not preclude the option of cost-minimisation with evolocumab for the higher alirocumab strength (150 mg fortnightly). The PBAC concluded that non-inferiority could only be supported for the up titrated dose of 150 mg fortnightly rather than on the analyses with the pooled doses of alirocumab.
- 7.9 The PBAC advised that alirocumab 150 mg fortnightly is equi-effective to evolocumab 140 mg fortnightly or 420 mg monthly. The PBAC, whilst noting the sponsor's request for flat pricing, advised that a tiered pricing structure reflecting the recommended equi-effective doses would be appropriate in light of the uncertainty with the lower doses of alirocumab (75 mg fortnightly or 300 mg monthly).
- 7.10 The PBAC noted that no significant safety issues were identified, with injection site reactions being minor, and therefore considered that non-inferior safety of alirocumab versus evolocumab was reasonable.

- 7.11 The PBAC noted the DUSC concerns about underestimation of the he-FH population and considered alirocumab should join the evolocumab risk sharing arrangement and that there should be no net cost to Government.
- 7.12 The PBAC advised that, like evolocumab, alirocumab is not suitable for prescribing by Nurse Practitioners.
- 7.13 The PBAC advised that alirocumab should not be exempt from the Early Supply Rule.
- 7.14 The PBAC advised, under section 101 (3BA) of the National Health Act, that alirocumab should be treated as interchangeable on an individual patient basis with evolocumab at the recommended equi-effective doses of alirocumab 150 mg fortnightly being equi-effective to evolocumab 140 mg fortnightly or 420 mg monthly.

**Outcome:**

Recommended

***Non-Familial hypercholesterolaemia (non-FH) with acute coronary syndrome (ACS) and diabetes***

- 7.15 The PBAC acknowledged there is a high unmet clinical need for patients with non-FH with high cardiovascular risk who are not adequately controlled with available lipid-lowering therapies, but considered that this population remains inadequately defined. The PBAC reiterated its previous advice that a PBS restriction for the non-FH population would require specific definitions of ASCVD and statin intolerance.
- 7.16 The PBAC considered the subgroup identified in this submission with ACS (previous ACS and recent ACS), diabetes and LDL-C  $\geq 2.6$  mmol/L were at relatively high risk of a CV event compared to the broader ITT population in the ODYSSEY OUTCOMES trial. However, a more directly defined population at high CV risk, considered to be an approximate 25% risk of a major CV event over 3 years, should be identified. The PBAC suggested exploring outcomes and cost-effectiveness for patients who: have experienced  $\geq 2$  events in  $\geq 2$  vascular territories over a short period of time; or have recent ACS and other high risk criteria such as diabetes mellitus; or who have other combinations of high risk criteria such as those identified in the current PBS listing for ezetimibe. The PBAC also considered that exploration of secondary prevention predictive models, such as the PREDICT CVD secondary prevention score, that predict a risk of  $>25\%$  over 3 years is an alternative or complementary approach.
- 7.17 The PBAC considered placebo, the nominated main comparator in patients with non-FH with previous ACS and concomitant diabetes, to be appropriate. The PBAC agreed with the ESC that, whilst the resubmission did not consider evolocumab as a potential near market comparator, the ITC of the CV outcomes trials (in patients with non-FH) was informative and indicated similar results for the composite CV outcomes across the ODYSSEY OUTCOMES and FOURIER trials.
- 7.18 The PBAC noted the ODYSSEY OUTCOMES trial provided direct outcomes data for the non-FH population and considered that the data supports the claim of superior efficacy versus placebo, despite some concerns over convergence in cardiovascular

event rates and attenuation of LDL reduction over time. The pre-PBAC response presented additional analyses of time to first occurrence of MACE using the subgroup of patients with LDL-C  $\geq$  2.6 mmol/L, which showed a continued divergence of the curves. However, the PBAC agreed with the ESC that the pattern of convergence in the ITT population remained inadequately explained. There was no similar convergence observed in the FOURIER trial. The PBAC considered the alirocumab findings were not adequately explained by the dosing algorithm that allowed for down-titrations and/or switching to placebo and the use of LDL targets (between 0.78 to 1.29 mmol/L) in the ODYSSEY OUTCOMES trial.

7.19 The PBAC noted the high and uncertain ICER (\$45,000/QALY to \$75,000/QALY) gained in the base case comparison with placebo. The PBAC had concerns regarding the validity of the model given the following:

- The proposed subgroup population (with a higher baseline risk than the overall trial population) was a key driver of the model, whilst the additional patient subgroup from the proposed indication that were statin intolerant were excluded.
- Use of the lower HR of [REDACTED], rather than 0.85, which was uncertain; the confidence intervals were relatively wide given this is a post-hoc subgroup analysis making the point estimate less reliable.
- Inappropriate use of Framingham risk equations to estimate the distribution of cardiac events in secondary prevention.
- The extrapolated treatment benefit out to 41 years was optimistic, with the ICER at 20 years being \$45,000 to \$75,000. The PBAC considered that a time horizon of 30 years would be more appropriate.
- As for the evolocumab resubmission in July 2018, while there is a biological plausibility of a reduction in CV mortality, there was no direct data to support the length of the time lag or the magnitude of the reduction in cardiovascular mortality in secondary prevention of CAD, and the approach to modelling of this outcome was questionable.

7.20 The PBAC noted the difficulties in defining a high-risk non-FH population with greatest benefit as outlined by the DUSC and considered revised financial estimates for the non-FH population only, including a more targeted high risk eligible population and reduced price to achieve a lower ICER, would need to address these concerns.

7.21 The PBAC considered a resubmission should include the following:

- Adjustment of the economic model based on the concerns raised in paragraph 7.19 in order to determine how to adjust the price. The PBAC considered the ICER would need to be lower than proposed in the current submission given the inherent uncertainties associated with estimating the number of events, including deaths, beyond the trial follow-up.

- Refinement of the proposed non-FH population to include those at highest risk of a cardiovascular event with an established risk level of 25% over 3 years. The PBAC advised that the high-risk group may include patients who have experienced  $\geq 2$  events in  $\geq 2$  vascular territories over a short period of time; or have recent ACS and other high risk criteria such as diabetes mellitus; or who have other combinations of high risk criteria such as those identified in the current PBS listing for ezetimibe.
- Alternative modelling approaches that are not informed by the primary prevention Framingham risk equations should be considered in any resubmission. This may include using a secondary prevention risk database with a predictive equation, or a robust subgroup from the outcome studies.
- The model structure should allow changes in baseline risk and treatment effect to be assessed more readily in sensitivity analyses.

7.22 The PBAC noted that this submission is not eligible for an Independent review. Where a submission is made to PBAC for multiple indications and PBAC recommends any of the requested indications, those indications not recommended by PBAC will not be eligible for independent review on that occasion

**Outcome:**

Rejected

Recommended listing

**Heterozygous familial hypercholesterolaemia (he-FH)**

**Add new item and amend evolocumab restriction for He-FH:**

Name, Restriction, Manner of administration and form	Max. Qty (pack)	No. of Rpts	Proprietary Name and Manufacturer	
ALIROCUMAB 75mg/mL injection, 2 x 1mL pre-filled pen	1	5	Praluent	Sanofi-Aventis
ALIROCUMAB 150mg/mL injection, 2 x 1mL pre-filled pen	1	5	Praluent	Sanofi-Aventis

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>PBS Indication:</b>	Familial heterozygous hypercholesterolaemia
<b>Treatment phase:</b>	Initial treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required – Electronic <input type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>The treatment must be in conjunction with dietary therapy and exercise  <b>AND</b>            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 6,  <b>AND</b>            Patient must have an LDL cholesterol level in excess of 3.3 millimoles per litre in the presence of symptomatic atherosclerotic cardiovascular disease; OR            Patient must have an LDL cholesterol level in excess of 5 millimoles per litre,  <b>AND</b>            Patient must have been treated with the maximum recommended dose of atorvastatin or rosuvastatin according to the TGA-approved Product Information for at least 3 months in conjunction with dietary therapy and exercise; OR            Patient must have developed clinically important product-related adverse events necessitating withdrawal of statin treatment to trials of each of atorvastatin and rosuvastatin; OR            Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information,  <b>AND</b>            Patient must have been treated with ezetimibe for at least 3 months in conjunction with dietary therapy and exercise.  <b>AND</b>            Patient must commence initial treatment on a dose of 75mg per fortnight or 300mg per month.  <b>AND</b>            Patient must not be receiving concomitant PBS-subsidised evolocumab.</p>

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<p><b>Treatment criteria:</b></p>	<p>Must be treated by a specialist physician.</p>
<p><b>Prescriber Instructions</b></p>	<p>A clinically important product-related adverse event is defined as follows:            (i) Severe myalgia (muscle symptoms without creatine kinase elevation) which is proven to be temporally associated with statin treatment; or            (ii) Myositis (clinically important creatine kinase elevation, with or without muscle symptoms) demonstrated by results twice the upper limit of normal on a single reading or a rising pattern on consecutive measurements and which is unexplained by other causes; or            (iii) Unexplained, persistent elevations of serum transaminases (greater than 3 times the upper limit of normal) during treatment with a statin.</p> <p>Symptomatic atherosclerotic cardiovascular disease is defined as:            (i) the presence of symptomatic coronary artery disease; or            (ii) the presence of symptomatic cerebrovascular disease; or            (iii) the presence of symptomatic peripheral vascular disease.</p> <p>The date of the consultation with a specialist physician must be no more than 6 months prior to the application date. The full name of the specialist physician consulted and the date of consultation are to be provided at the time of application.</p> <p>The qualifying LDL cholesterol level must be provided at the time of application and must be no more than 2 months old.</p> <p>The physician must attempt to treat the patient with the maximum recommended dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily).</p> <p>If treatment with atorvastatin or rosuvastatin results in development of a clinically important product-related adverse event resulting in treatment withdrawal, the patient must be treated with the alternative statin (atorvastatin or rosuvastatin). This retreatment should occur after a washout period of at least 1 month, or if the creatine kinase (CK) level is elevated retreatment should not occur until CK has returned to normal.</p> <p>In the event of a trial of an alternative statin, it is recommended that the patient is started with the minimum dose of statin in conjunction with ezetimibe. The dose of the alternative statin should be increased not more often than every 4 weeks until the maximum tolerated dose has been reached or target LDL-c has been achieved.</p> <p>At the time of application, one of the following must be provided:            (i) Confirmation that the patient was treated with atorvastatin 80 mg or rosuvastatin 40 mg for 3 months; or            (ii) The doses and duration of treatment and adverse events experienced with trials with each of atorvastatin and rosuvastatin; or            (iii) Confirmation that the patient is contraindicated to treatment with a statin as defined in the TGA-approved Product Information.</p> <p>The authority application must be made in writing and must include:            a) A completed authority prescription form; and            b) A completed Familial Hypercholesterolaemia Initial PBS Authority Application - Supporting Information Form; and            c) The date of consultation and the full name of the consultant physician; and            d) A copy of the qualifying Dutch Lipid Clinic Network Score or a copy of the result of genetic testing; and</p>

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	e) The result of LDL cholesterol level and one of the following where appropriate: statin treatment details including agent, dose and treatment duration; or details of adverse event or contraindication to treatment with a statin as defined in the TGA-approved Product Information.
<b>Administrative Advice</b>	<p>No increase in the maximum quantity or number of units may be authorised.          No increase in the maximum number of repeats may be authorised.          Special Pricing Arrangements apply.</p> <p><b>Note</b>          Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).          Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a>          Applications for authority to prescribe should be forwarded to:          Department of Human Services          Complex Drugs          Reply Paid 9826          HOBART TAS 7001</p>

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>PBS Indication:</b>	Familial heterozygous hypercholesterolaemia
<b>Treatment phase:</b>	Continuing treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required – Electronic <input type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition, <b>AND</b></p> <p>The treatment must be in conjunction with dietary therapy and exercise</p>
<b>Administrative Advice</b>	<p><b>Note</b>          Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>No increase in the maximum quantity or number of units may be authorised.          No increase in the maximum number of repeats may be authorised.          Special Pricing Arrangements apply.</p>

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<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>PBS Indication:</b>	Familial heterozygous hypercholesterolaemia
<b>Treatment phase:</b>	Grandfather treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required – Electronic <input type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [PBS listing date],</p> <p><b>AND</b></p> <p>The treatment must be in conjunction with dietary therapy and exercise,</p> <p><b>AND</b></p> <p>The condition must have been confirmed by genetic testing; OR</p> <p>The condition must have been confirmed by a Dutch Lipid Clinic Network Score of at least 6,</p> <p><b>AND</b></p> <p>Patient must have had an LDL cholesterol level in excess of 3.3 millimoles per litre in the presence of symptomatic atherosclerotic cardiovascular disease at the time non-PBS subsidised treatment with this drug for this condition was initiated; OR</p> <p>Patient must have had an LDL cholesterol level in excess of 5 millimoles per litre at the time non-PBS subsidised treatment with this drug for this condition was initiated,</p> <p><b>AND</b></p> <p>Patient must have been treated with the maximum tolerated dose of atorvastatin or rosuvastatin according to the TGA-approved Product Information for at least 3 months in conjunction with dietary therapy and exercise prior to initiating non-PBS subsidised treatment with this drug for this condition, OR</p> <p>Patient must have developed clinically important product-related adverse events necessitating withdrawal of statin treatment to trials of each of atorvastatin and rosuvastatin prior to initiating non-PBS subsidised treatment with this drug for this condition, OR</p> <p>Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information.</p>
<b>Treatment criteria:</b>	Must be treated by a specialist physician.
<b>Prescriber Instructions</b>	<p>A clinically important product-related adverse event is defined as follows:</p> <p>(i) Severe myalgia (muscle symptoms without creatine kinase elevation) which is proven to be temporally associated with statin treatment; or</p> <p>(ii) Myositis (clinically important creatine kinase elevation, with or without muscle symptoms) demonstrated by results twice the upper limit of normal on a single reading or a rising pattern on consecutive measurements and which is unexplained by other causes; or</p> <p>(iii) Unexplained, persistent elevations of serum transaminases (greater than 3 times the upper limit of normal) during treatment with a statin.</p>

	<p>Symptomatic atherosclerotic cardiovascular disease is defined as:                  (i) the presence of symptomatic coronary artery disease; or                  (ii) the presence of symptomatic cerebrovascular disease; or                  (iii) the presence of symptomatic peripheral vascular disease.</p> <p>The date of the consultation with a specialist physician must be no more than 6 months prior to the application date. The full name of the specialist physician consulted and the date of consultation are to be provided at the time of application.</p> <p>The qualifying LDL cholesterol level must be provided at the time of application and must have been no more than 2 months old at the time non-PBS subsidised treatment with this drug for this condition was initiated.</p> <p>If the patient has developed a clinically important product-related adverse event, the clinician must confirm at the time of the application that the maximum tolerated dose of atorvastatin or rosuvastatin has been trialled and has resulted in the patient developing a clinically important product-related adverse event resulting in treatment withdrawal.</p> <p>If treatment with atorvastatin or rosuvastatin results in development of a clinically important product-related adverse event resulting in treatment withdrawal, the patient must be treated with the alternative statin (atorvastatin or rosuvastatin). This retriial should occur after a washout period of at least 1 month, or if the creatine kinase (CK) level is elevated retriial should not occur until CK has returned to normal.</p> <p>In the event of a trial of an alternative statin, the dose of the alternative statin should be increased not more often than every 4 weeks until the maximum tolerated dose has been reached or target LDL-c has been achieved.</p> <p>With the exception of the situation where the patient is contraindicated to treatment with a statin, the doses and duration of treatment and adverse events experienced with trials with each of atorvastatin and rosuvastatin must be provided at the time of application.</p> <p>Contraindication to treatment with a statin is as defined in the TGA-approved Product Information.</p> <p>The authority application must be made in writing and must include:                  a) A completed authority prescription form; and                  b) A completed Familial Hypercholesterolaemia Grandfather PBS Authority Application - Supporting Information Form; and                  c) The date of consultation and the full name of the consultant physician; and                  d) A copy of the qualifying Dutch Lipid Clinic Network Score or a copy of the result of genetic testing; and                  e) The result of LDL cholesterol level and one of the following where appropriate: statin treatment details including agent and dose; or details of adverse event or contraindication to treatment with a statin as defined in the TGA-approved Product Information.</p> <p>A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.</p>
<p><b>Administrative Advice</b></p>	<p><b>Note</b>                  Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p>

	<p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></p> <p>Applications for authority to prescribe should be forwarded to:                  Department of Human Services                  Complex Drugs                  Reply Paid 9826                  HOBART TAS 7001</p>
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7.23 Add extra clinical criterion for evolocumab restriction for He-FH:

<b>Clinical criteria:</b>	<p><b>AND</b>                  Patient must not be receiving concomitant PBS-subsidised alirocumab.</p>
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## 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 recommendation to list alirocumab for He-FH. We will continue to work with the PBAC to obtain reimbursement for alirocumab for non-FH patients with high cardiovascular risk who are not adequately controlled with available lipid-lowering therapies in recognition of high unmet clinical need for effective treatments.