

An addendum to this Public Summary Document (PSD) has been included at the end of the document.

**5.08 INCLISIRAN,
Injection 284 mg in 1.5 mL single use pre-filled
syringe,
Leqvio[®],
Novartis Pharmaceuticals Australia Pty Limited.**

1 Purpose of submission

- 1.1 The Category 2 submission requested a General Schedule (Section 85) Authority Required (STREAMLINED) listing of inclisiran for the treatment of hypercholesterolaemia and atherosclerotic cardiovascular disease (ASCVD). The PBAC has not previously considered inclisiran for any indication.
- 1.2 The submission claimed that while there are effective treatments for hypercholesterolaemia available under the PBS, there remains a clinical need for more effective lipid-lowering therapies in the second-line setting (without the need to first fail ezetimibe therapy) that may avoid the need for more costly therapies in the subsequent line setting (i.e. proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors). The submission also noted the need for access to therapies with a lower treatment burden (6-monthly injections for maintenance dosing with inclisiran) compared to existing medications (fortnightly/monthly injections for PCSK9 inhibitors) in the subsequent-line setting.
- 1.3 Listing was requested on the basis of a cost-effectiveness analysis versus ezetimibe followed by PCSK9 inhibitor therapies in the second/subsequent-line treatment setting. The submission also presented a cost-minimisation analysis (CMA) versus PCSK9 inhibitor therapies in the subsequent-line treatment setting, although the 'placeholder' effective price requested is based on the cost-effectiveness analysis.

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

Component	Description
Population	Patients with hypercholesterolaemia and atherosclerotic cardiovascular disease who have additional cardiovascular risk factors and who are unable to achieve target lipid thresholds with statins alone or who are intolerant to statin therapy
Intervention	Inclisiran 284 mg subcutaneous injection administered at Day 1, followed by a subsequent injection at 3 months and then every 6 months.
Comparator	Second-line: Ezetimibe 10 mg tablet administered once daily. Subsequent line: Evolocumab 140 mg subcutaneous injection administered fortnightly or 420 mg subcutaneous injection administered monthly. Alirocumab 75 or 150 mg subcutaneous injection administered fortnightly (titratable dose) or 300 mg subcutaneous injection administered monthly
Outcomes	Reduction in LDL-C leading to a reduction in major cardiovascular events (e.g. cardiovascular death, myocardial infarction, stroke), incidence of adverse events
Clinical claim	Inclisiran is superior in terms of efficacy and non-inferior in terms of safety compared to ezetimibe Inclisiran is non-inferior in terms of efficacy and safety compared to evolocumab and alirocumab

Source: Table 1; Attachment 4; Attachment 11 of the submission

Abbreviations: LDL-C, low density lipoprotein cholesterol

1.4 The ESC considered the proposed positioning of inclisiran as a second-line alternative to ezetimibe was not justified for multiple reasons:

- A very large number of patients who would otherwise achieve their low density lipoprotein cholesterol (LDL-C) target on a statin and ezetimibe combination would instead take a statin and inclisiran combination at a much higher drug acquisition cost.
- The treatment burden is higher with a statin and inclisiran than with a statin and ezetimibe, i.e. a daily tablet and an injection, even if only every 6 months, rather than a daily fixed dose oral combination.
- There are many potential variables and uncertainties in the eligible patient population, the long-term effectiveness and safety of inclisiran, the uptake rates and the financial estimates that any significant shift in the current treatment algorithm for treating elevated LDL-C is inadequately justified in this submission.
- The treatment algorithm as proposed by the sponsor is not supported by any national or international treatment guidelines. The American College of Cardiology (ACC) 2022 consensus statement positions inclisiran for patients with demonstrated poor adherence or intolerance to PCSK9 inhibitor therapy (see paragraph 4.7).

1.5 The pre-PBAC response, noting the above concerns regarding the proposed second-line listing, stated that inclisiran could be positioned as a non-inferior alternative to the PCSK9 inhibitors in the third line setting for patients with ASCVD and heterozygous familial hypercholesterolaemia (HeFH).

1.6 Sections 1-6 below include the submission's proposed second-line setting.

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

2 Background

Registration status

2.1 Inclisiran was approved by the TGA on 14 September 2021 as an adjunct to diet and exercise to reduce low-density lipoprotein (LDL) cholesterol in adults with heterozygous familial hypercholesterolaemia, atherosclerotic cardiovascular disease, or at high risk of a cardiovascular event:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL goals with the maximum tolerated dose of a statin, or
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Maximum Quantity	Max. qty packs	Max. qty units	No. of Rpts	Available brands
INCLISIRAN					
INITIAL					
Inclisiran, prefilled syringe 284 mg/1.5 mL, 1	\$2,847.78 published price \$ [REDACTED] effective price	1	1	1	Leqvio
CONTINUING					
Inclisiran, prefilled syringe 284 mg/1.5 mL, 1	\$2,847.78 published price \$ [REDACTED] effective price	1	1	0	Leqvio
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: ☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives					
PBS Indication: Hypercholesterolaemia					
Restriction: ☒ Streamlined					
CLINICAL CRITERIA FOR INITIAL THERAPY					
Clinical criteria:					
The treatment must be in conjunction with dietary therapy and exercise					
AND					
Clinical criteria:					
Patient must have symptomatic high risk atherosclerotic cardiovascular disease					
AND					
Clinical criteria:					
Patient must have an LDL cholesterol level in excess of 1.8 mmol/L; OR					
Patient must be currently treated with ezetimibe					
AND					
Clinical criteria:					
Patient must have atherosclerotic disease in two or more vascular territories (coronary, cerebrovascular or peripheral vascular territories); OR					
Patient must have severe multi-vessel coronary heart disease defined as at least 50% stenosis in at least two large vessels; OR					
Patient must have had at least two major cardiovascular events (i.e. myocardial infarction, unstable angina, stroke or unplanned revascularisation) in the previous 5 years; OR					

Public Summary Document - March 2023 PBAC Meeting with May 2023 Addendum

Patient must have diabetes mellitus with microalbuminuria; OR
Patient must have diabetes mellitus and be aged 60 years or more; OR
Patient must be an Aboriginal or Torres Strait Islander with diabetes mellitus; OR
Patient must have a Thrombolysis in Myocardial Infarction (TIMI) risk score for secondary prevention of 4 or higher;
AND
Clinical criteria:
Patient must have been treated with the maximum recommended dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily) according to the TGA-approved Product Information or the maximum tolerated dose of atorvastatin or rosuvastatin for at least 12 consecutive weeks 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
CLINICAL CRITERIA FOR CONTINUING THERAPY
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
The treatment must be in conjunction with dietary therapy and exercise
Prescriber Instructions: Must be treated by or in consultation with a specialist physician
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.

Source: Table 8; Table 9; Table 10; Table 11 of the submission.

- 3.1 The submission requested a special pricing arrangement. The submission included a 'placeholder' effective price for inclisiran but noted that the economic analyses were dependent on the price of evolocumab and alirocumab which are both subject to special pricing arrangements. The submission stated that the placeholder price would need to be adjusted once the effective prices for PCSK9 inhibitors are made known to the sponsor. The submission stated that the intent of the effective price was to be sufficiently lower than PCSK9 inhibitors in order for inclisiran to be a cost-effective treatment option in the second-line setting.
- 3.2 The submission stated that the proposed PBS restriction for inclisiran was modelled on existing restrictions for evolocumab and alirocumab when used as subsequent-line therapies in patients with non-familial hypercholesterolaemia (non-FH) (including the recent PBAC recommendation to lower the LDL-C criterion and permit GP prescribing in consultation with a specialist; evolocumab PSD, July 2022 PBAC meeting). The submission noted that the restriction was further modified to account for the proposed role of inclisiran as a second-line alternative to ezetimibe treatment. The ESC noted the restriction using criteria from current PCSK9 inhibitor therapies was broadly appropriate; however, the difference with the ezetimibe restriction may create confusion for prescribers as to whether patients are eligible for inclisiran or only ezetimibe in the second line.
- 3.3 The requested Streamlined Authority level may not be appropriate, given the clinical criteria and accompanying notes for inclisiran are complex and substantially more

restrictive than the clinical criteria for ezetimibe. The PCSK9 inhibitors currently subsidised on the PBS (evolocumab and alirocumab) for subsequent-line therapy have an Authority Required (telephone/online) listing for initial scripts and a Streamlined Authority for continuing scripts in order to reduce the potential for use outside the requested restriction. A similar authority level may also be appropriate for inclisiran. The Pre-Sub-Committee Response (PSCR) offered changing the proposed restriction to an Authority Required (telephone/online) listing for the initial supply scripts and Streamlined Authority for continuing scripts.

- 3.4 The submission requested to exclude LDL qualifying criteria from the proposed restriction for patients already treated with ezetimibe given that the current PBS listing for ezetimibe is agnostic to specific LDL cholesterol values. The DUSC and ESC considered this was not appropriate as it would provide a pathway to bypass all LDL-C requirements currently required for any PCSK9 inhibitor therapy and allow treatment in populations for which cost-effectiveness has not yet been demonstrated (i.e. in patients with baseline LDL < 1.8 mmol/L).
- 3.5 The proposed restriction does not allow familial hypercholesterolaemia to be considered as a qualifying high-risk factor for patients with atherosclerotic disease, which is inconsistent with other PBS listings. Additionally, all existing PBS subsidised hypercholesterolaemia therapies can be used for the primary prevention of cardiovascular events in familial hypercholesterolaemia populations. This population was not requested in the submission and the justification for excluding this population was unclear given that the ORION-9 trial was conducted in a HeFH population and inclisiran is TGA-approved for use in this population. The PSCR suggested including diagnosed familial hypercholesterolaemia as a qualifying high-risk factor for patients with ASCVD to the proposed restriction. The ESC advised that the addition of diagnosed HeFH as a high-risk factor in ASCVD patients may be appropriate, however it affects the applicability of the modelled population and the treatment effect being modelled, as the ORION-9 trial in HeFH patients would be relevant. Inclisiran is not registered for use in homozygous familial hypercholesterolaemia.
- 3.6 The submission requested listing of inclisiran as a monotherapy and as part of non-statin combination therapy (e.g. with ezetimibe) in patients who are statin-intolerant. However, the submission did not provide any comparative data in statin-intolerant patients which is a significant limitation given the extensive body of evidence supporting the use of both evolocumab and alirocumab in this population (see paragraph 6.14).
- 3.7 The proposed restriction did not include any criteria preventing the use of inclisiran in combination with existing PCSK9 inhibitors. This was inappropriate as there are no clinical data nor any mechanistic plausibility to support combination therapy. The PSCR supported the addition of a criterion preventing the use of inclisiran in combination with PCSK9 inhibitors.

- 3.8 The submission requested a grandfathered listing for patients currently enrolled in the Australian VICTORION-ASCERTAIN trial as well as patients enrolled in a patient familiarisation program that would be initiated if inclisiran receives a positive PBAC recommendation (planned size of approximately 500 to < 5,000 patients).

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

4 Population and disease

- 4.1 Hypercholesterolaemia is a common condition characterised by elevated serum cholesterol levels. The causes of hypercholesterolaemia can include both genetic and environmental factors (e.g. diet and lifestyle) although the vast majority of patients with hypercholesterolaemia have elevated cholesterol levels in the absence of any specific genetic disorder.
- 4.2 A minority of patients have an autosomal dominant inherited disorder that affects receptor-mediated uptake of LDL cholesterol resulting in high cholesterol levels. The mutation is most frequently inherited from one parent (HeFH) or more rarely from both parents, which results in a more severe manifestation of the disorder (homozygous familial hypercholesterolaemia, HoFH). Patients with familial hypercholesterolaemia are exposed to elevated cholesterol levels from birth and typically have very high LDL-C levels.
- 4.3 Hypercholesterolaemia is associated with the development of atherosclerosis and an increased incidence of angina, myocardial infarction, stroke, coronary artery disease and peripheral vascular disease. These cardiovascular events can have major impact on survival, quality of life and future risk of further cardiovascular events.
- 4.4 Inclisiran is a small interference RNA (siRNA) that operates as a 'gene silencer', inhibiting the translation of PCSK9 in the liver cell, which prevents the degradation of the LDL receptor on the cell surface, leading to a reduction of LDL cholesterol.
- 4.5 The clinical management algorithm positioned inclisiran as a second-line alternative to ezetimibe in a subset of patients with atherosclerotic disease and additional cardiovascular risk factors who are unable to achieve target lipid thresholds with statins alone or who are intolerant to statin therapy. The algorithm lacked sufficient detail of the subsequent line treatment setting, in particular the role of inclisiran and ezetimibe in this setting. Based on other parts of the submission the sponsor assumed inclisiran would be an alternative to PCSK9 inhibitors in the subsequent-line setting and assumed that subsequent-line PCSK9 inhibitor treatment would replace second-line ezetimibe rather than be used as an additional therapy. The ESC considered that the place in therapy proposed in the submission, as a second-line alternative to ezetimibe, was not justified (see paragraph 1.4). The ESC considered that inclisiran would be most appropriately positioned as an alternative to the PCSK9s inhibitors, due to its different mechanism of action in the inhibition of PCSK9, in the subsequent treatment line to statin and/or ezetimibe.

- 4.6 The submission noted that the introduction of more effective agents (such as PCSK9 monoclonal antibodies) has allowed the adoption of more aggressive treatment targets for LDL-C lowering in the treatment guidelines. Recent international guidelines note that there is currently no defined level of LDL-C below which benefit ceases or harm occurs. The submission expects that the updated Australian guidelines will also adopt similarly aggressive LDL-C targets.
- 4.7 The 2022 American College of Cardiology (ACC) consensus statement was the only report to explicitly include inclisiran in the recommendations. The report stated that PCSK9 monoclonal antibodies remain the preferred PCSK9 inhibitor choice given the demonstrated safety, efficacy and cardiovascular outcome data for these therapies compared to inclisiran. However, the ACC consensus stated that inclisiran may be considered in patients with demonstrated poor adherence to PCSK9 monoclonal antibodies, patients with adverse effects from PCSK9 monoclonal antibodies or those who may be unable to self-inject. The report noted that there is currently no evidence or mechanistic plausibility for additional efficacy in LDL-C lowering or cardiovascular outcomes from combination therapy with a PCSK9 monoclonal antibody and inclisiran. Therefore, the ACC consensus states that if inclisiran is to be used, it should be used in place of a PCSK9 monoclonal antibody.

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

5 Comparator

- 5.1 The submission nominated ezetimibe as the main comparator in the second line setting and PCSK9 inhibitor therapies as the main comparators in the subsequent-line treatment setting. The ESC considered that the nominated comparators were appropriate for the proposed treatment lines. However, if the place in therapy is as an alternative to PCSK9 inhibitors, evolocumab and alirocumab are the appropriate comparators, and ezetimibe would not need to be considered.
- 5.2 The main differences between inclisiran, ezetimibe, evolocumab and alirocumab are:
- Inclisiran is a small interference RNA therapy that targets PCSK9. Evolocumab and alirocumab are monoclonal antibodies that target PCSK9. Ezetimibe is a conventional small molecule therapy that targets NPC1L1.
 - Inclisiran is administered as a subcutaneous injection by a healthcare professional. Evolocumab and alirocumab are self-administered as subcutaneous injections. Ezetimibe is self-administered as an oral tablet.
 - Inclisiran, evolocumab and ezetimibe have fixed dosing regimens while alirocumab has a flexible dosing regimen (allowing titration-to-effect).
 - Inclisiran is administered once every 6 months (after the initial two doses at Day 1 and Month 3). Evolocumab and alirocumab are administered once fortnightly or monthly. Ezetimibe is administered once daily. Unless intolerant or

contra-indicated, patients receiving inclisiran, evolocumab, alirocumab and ezetimibe will also receive treatment with oral statin therapies.

- Ezetimibe is available as a fixed dose combination with statins while the other therapies are only available as single agents.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the need for new therapies to treat patients who remained sub-optimally controlled on currently available treatments. The clinician also described the durability of the LDL-C lowering treatment effect associated with inclisiran and the benefits associated with the 6-monthly dosing schedule which included improved adherence to therapy and the better management of patients, particularly those in rural and remote areas and older patients. The PBAC considered that the hearing was informative.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (3), health care professionals (1) and organisations (4) via the Consumer Comments facility on the PBS website. The comments described the benefits of treatment with inclisiran including the ease and quality of life benefits associated with twice yearly dosing and the need for alternate therapies for patients who are intolerant to currently available treatments.
- 6.3 The PBAC noted the advice received from the Familial Hypercholesterolaemia Australasia Network clarifying the likely use of inclisiran in clinical practice, particularly for patients with familial hypercholesterolaemia and high-risk cardiovascular patients with hypercholesterolaemia who are intolerant to statins and PCSK9 inhibitor therapies. Advice was also received from the Heart Foundation, Hearts 4 Hearts and Heartbeat of Football which noted the need for alternate therapies and the ease of administration associated with twice yearly injections. The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

- 6.4 No head-to-head trials comparing inclisiran with ezetimibe, evolocumab or alirocumab were identified. The submission was based on a series of indirect comparisons against nominated comparators:
- Indirect analyses of lipid outcomes with inclisiran (ORION-10, ORION-11) versus ezetimibe (ACCENTUATE, EASE) with placebo as the common reference in patients with ASCVD or ASCVD risk-equivalents.

- Indirect analyses of lipid outcomes with inclisiran (ORION-10, ORION-11) versus evolocumab (DESCARTES, LAPLACE-2, BANTING; or separate analyses using longer-term data from DESCARTES or FOURIER) with placebo as the common reference in patients with ASCVD or ASCVD risk-equivalents.
- Indirect analyses of lipid outcomes with inclisiran (ORION-9) versus evolocumab (RUTHERFORD-1, RUTHERFORD-2) with placebo as the common reference in patients with HeFH.
- Indirect analyses of lipid outcomes with inclisiran (ORION-10, ORION-11) versus alirocumab (COMBO-I, CHOICE-I, CHOICE-II, KT, INSULIN-DM, LONG-TERM; or separate analyses using longer-term data from LONG-TERM and/or OUTCOMES) with placebo as the common reference in patients with ASCVD or ASCVD risk-equivalents.
- Indirect analyses of lipid outcomes with inclisiran (ORION-9) versus alirocumab (FH-1, FH-2, HIGH-FH) with placebo as the common reference in patients with HeFH.

6.5 The submission also noted two ongoing cardiovascular outcome trials of inclisiran compared to placebo in patients with ASCVD (ORION-4 with estimated completion July 2026; VICTORION-2P with estimated completion in October 2027). These studies were excluded from the submission as no results were available.

6.6 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Inclisiran trials		
ORION 9	The Medicines Company (2019). A placebo-controlled, double-blind, randomized trial to evaluate the effect of 300 mg of inclisiran sodium given as subcutaneous injections in subjects with heterozygous familial hypercholesterolemia (HeFH) and elevated low density lipoprotein cholesterol (LDL-C)	Internal study report
	Raal FJ et al (2020). Inclisiran for the treatment of heterozygous familial hypercholesterolemia.	New England Journal of Medicine 382(16):1520-30.
ORION 10	The Medicines Company (2019). A placebo-controlled, double-blind, randomized trial to evaluate the effect of 300 mg of inclisiran sodium given as subcutaneous injections in subjects with atherosclerotic cardiovascular disease (ASCVD) and elevated low density lipoprotein cholesterol (LDL-C)	Internal study report
	Ray KK et al (2020). Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol.	New England Journal of Medicine 382(16):1507-19.
ORION 11	The Medicines Company (2019). A placebo-controlled, double-blind, randomized trial to evaluate the effect of 300 mg of inclisiran sodium given as subcutaneous injections in subjects with atherosclerotic cardiovascular disease (ASCVD) or ASCVD risk equivalents and elevated low density lipoprotein cholesterol (LDL-C)	Internal study report
	Ray KK et al (2020). Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol.	New England Journal of Medicine 382(16):1507-19.

Public Summary Document - March 2023 PBAC Meeting with May 2023 Addendum

Trial ID	Protocol title/ Publication title	Publication citation
Ezetimibe trials		
ACCENTUATE	Nicholls SJ et al (2017). Comparative effects of cholesteryl ester transfer protein inhibition, statin or ezetimibe on lipid factors: the ACCENTUATE trial.	Atherosclerosis 261:12-8.
EASE	Pearson TA et al (2005). A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the ezetimibe add-on to statin for effectiveness (EASE) trial.	Mayo Clinic Proceedings 80(5): 587-595.
Evolocumab trials		
RUTHERFORD-1	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 hypercholesterolemia: the Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) randomized trial.	Circulation 126(20):2408-17.
RUTHERFORD-2	Raal FJ et al (2015). PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial.	Lancet 385(9965):331-40.
DESCARTES	Blom DJ et al (2014). A 52-week placebo-controlled trial of evolocumab in hyperlipidemia.	New England Journal of Medicine 370:1809-19.
FOURIER	Sabatine MS et al (2017). Evolocumab and clinical outcomes in patients with cardiovascular disease.	New England Journal of Medicine 376(18):1713-22.
LAPLACE-2	Robinson JG et al (2014). Effect of evolocumab or ezetimibe added to moderate-or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial.	JAMA 311(18):1870-83.
BANTING	Rosenson RS et al (2019). Efficacy and safety of evolocumab in individuals with type 2 diabetes mellitus: primary results of the randomised controlled BANTING study.	Diabetologia 62(6):948-58.
Alirocumab trials		
ODYSSEY FH I ODYSSEY FH II	Kastelein JJ et al (2015). ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia.	European Heart Journal 36(43):2996-3003.
ODYSSEY HIGH FH	Ginsberg HN 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(5):473-83.
ODYSSEY CHOICE I	Roth EM et al (2016). A phase III randomized trial evaluating alirocumab 300 mg every 4 weeks as monotherapy or add-on to statin: ODYSSEY CHOICE I.	Atherosclerosis 254:254-62.
ODYSSEY CHOICE II	Stroes E et al (2016). Efficacy and safety of alirocumab 150 mg every 4 weeks in patients with hypercholesterolemia not on statin therapy: the ODYSSEY CHOICE II study.	Journal of the American Heart Association 5(9):e003421.
ODYSSEY COMBO I	Kereiakes DJ et al (2015). Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: the ODYSSEY COMBO I study.	American Heart Journal 169(6):906-15.
ODYSSEY LONG TERM	Robinson JG et al (2015). Efficacy and safety of alirocumab in reducing lipids and cardiovascular events.	New England Journal of Medicine 372(16):1489-99.
ODYSSEY KT	Koh KK et al (2018). A randomized trial evaluating the efficacy and safety of alirocumab in South Korea and Taiwan (ODYSSEY KT).	Journal of Clinical Lipidology 12(1):162-72.
ODYSSEY DM-INSULIN	Leiter LA et al (2017). Efficacy and safety of alirocumab in insulin - treated individuals with type 1 or type 2 diabetes and high cardiovascular risk: the ODYSSEY DM - INSULIN randomized trial.	Diabetes and Metabolism Journal 19(12):1781-92.

Trial ID	Protocol title/ Publication title	Publication citation
ODYSSEY OUTCOMES	Schwartz GG et al (2018). Alirocumab and cardiovascular outcomes after acute coronary syndrome.	New England Journal of Medicine 379(22):2097-107.

Source: Table 16 of the submission; Table 1 Attachment 4 of the submission.

6.7 The key features of the included inclisiran trials are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Inclisiran versus placebo						
ORION-9	482	MC, R, DB, PC 540 days	Low	HeFH	Change in LDL-C levels	Subgroup used to inform baseline risk
ORION-10	1,561	MC, R, DB, PC 540 days	Low	Hypercholesterolaemia with ASCVD	Change in LDL-C levels	Overall trial results inform treatment efficacy, subgroup used to inform baseline risk and discontinuations
ORION-11	1,617	MC, R, DB, PC 540 days	Low	Hypercholesterolaemia with ASCVD or risk equivalent	Change in LDL-C levels	Subgroup used to inform baseline risk and discontinuations

Source: Section 2.4 of the submission

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; DB, double-blind; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; MC, multicentre; PC, placebo-controlled; R, randomised.

6.8 The PBAC has previously considered changes in LDL-C levels to be a reasonable surrogate for changes in cardiovascular outcomes in hypercholesterolaemia populations (PBAC Post Market Review of Ezetimibe, December 2017; alirocumab and evolocumab PSDs, multiple meetings) but has also noted the importance of having results from confirmatory cardiovascular outcome trials (alirocumab and evolocumab PSDs, multiple meetings). The ESC considered that, in the absence of trials with cardiovascular outcomes, change in LDL-C level was a reasonable surrogate. The PSCR noted since the lodging of the inclisiran submission, a patient-level, pooled analysis of ORION-9, -10 and -11 was published (Ray 2023) which reported that inclisiran significantly reduced composite MACE [OR = 0.74 (0.58–0.94)].¹

Comparative effectiveness

6.9 Meta-analyses of the co-primary LDL-C outcomes (mean percentage change in LDL-C from baseline to Day 510 and time-adjusted mean percentage change in LDL-C from baseline after Day 90 and up to Day 540) with inclisiran and placebo from the ORION trials are summarised in Table 4.

¹ Ray, Kausik K., et al. (2023) Inclisiran and cardiovascular events: a patient-level analysis of phase III trials. European Heart Journal 44.2: 129-138.

Table 4: Meta-analysis of co-primary LDL-C outcomes from the inclisiran trials

Trial	Inclisiran, Mean, % (SD)	Placebo, Mean, % (SD)	Treatment difference, Mean, % (95% CI)
Mean percentage change from baseline in LDL-C at Day 510 (primary - multiple imputation washout model)			
ORION 9, N = 482	-39.67 (31.47)	8.22 (30.66)	-47.89 (-53.52, -42.26)
ORION 10, N = 1,561	-51.28 (33.19)	0.96 (32.13)	-52.24 (-55.65, -48.83)
ORION 11, N = 1,617	-45.80 (33.02)	4.00 (31.55)	-49.90 (-53.07, -46.64)
Meta-analysis of ORION 10,11 ($I^2 = 1\%$)			-50.94 (-53.33, -48.56)
Meta-analysis of ORION 9,10 ($I^2 = 40\%$)			-50.65 (-54.76, -46.55)
Meta-analysis of ORION 9,11 ($I^2 = 0\%$)			-49.32 (-52.14, -46.50)
Meta-analysis of ORION 9,10,11 ($I^2 = 0\%$)			-50.48 (-52.67, -48.29)
Pooled IPD analysis of ORION 9,10,11 (Wright 2021)			-50.7 (-52.9, -48.4)
Mean percentage change from baseline in LDL-C at Day 510 (observed data)			
ORION 9, N = 482	-41.15 (-44.52, -37.77)	8.37 (3.96, 12.77)	-49.52 (-55.04, -43.99)
ORION 10, N = 1,561	-56.34 (-58.35, -54.34)	1.30 (-1.24, 3.83)	-57.64 (-60.86, -54.43)
ORION 11, N = 1,617	-49.30 (-51.22, -47.48)	4.20 (1.62, 6.69)	-53.50 (-56.66, -50.35)
Meta-analysis of ORION 10,11 ($I^2 = 69\%$)			-55.55 (-59.61, -51.50)
Meta-analysis of ORION 9,10 ($I^2 = 84\%$)			-53.91 (-61.84, -45.97)
Meta-analysis of ORION 9,11 ($I^2 = 33\%$)			-52.19 (-55.86, -48.53)
Meta-analysis of ORION 9,10,11 ($I^2 = 72\%$)			-54.01 (-58.16, -49.85)
Mean percentage change from baseline in LDL-C at Day 510 (mixed effects model for repeated measures)			
ORION 9, N = 482	-40.76 (-44.63, -36.88)	8.06 (4.16, 11.96)	-48.82 (-54.32, -43.32)
ORION 10, N = 1,561	-56.17 (-58.36, -53.98)	1.07 (-1.15, 3.29)	-57.24 (-60.36, -54.13)
ORION 11, N = 1,617	-48.81 (-50.98, -46.64)	3.87 (1.71, 6.03)	-52.68 (-55.74, -49.62)
Meta-analysis of ORION 10,11 ($I^2 = 76\%$)			-54.95 (-59.42, -50.48)
Meta-analysis of ORION 9,10 ($I^2 = 85\%$)			-53.35 (-61.58, -45.12)
Meta-analysis of ORION 9,11 ($I^2 = 31\%$)			-51.45 (-54.98, -47.93)
Meta-analysis of ORION 9,10,11 ($I^2 = 76\%$)			-53.34 (-57.71, -48.96)
Time-adjusted mean percentage change in LDL-C from baseline after Day 90 and up to Day 540 (primary – pattern mixture model)			
ORION 9, N = 482	-38.08 (-41.03, -35.14)	6.22 (3.26, 9.17)	-44.30 (-48.48, -40.12)
ORION 10, N = 1,561	-51.27 (-53.00, -49.54)	2.51 (0.77, 4.25)	-53.78 (-56.23, -51.33)
ORION 11, N = 1,617	-45.82 (-47.52, -44.13)	3.35 (1.65, 5.05)	-49.17 (-51.57, -46.77)
Meta-analysis of ORION 10,11 ($I^2 = 86\%$)			-51.47 (-55.99, -46.95)
Meta-analysis of ORION 9,10 ($I^2 = 93\%$)			-49.20 (-58.48, -39.91)
Meta-analysis of ORION 9,11 ($I^2 = 75\%$)			-47.05 (-51.78, -42.31)
Meta-analysis of ORION 9,10,11 ($I^2 = 88\%$)			-49.33 (-54.12, -44.54)
Pooled IPD analysis of ORION 9,10,11 (Wright 2021)			-50.5 (-52.1, -48.9)

Source: Figure 15; Figure 17 of the submission; Figure 2 of the Wright 2021 publication

Abbreviations: IPD, individual patient data; LDL-C, low density lipoprotein cholesterol

Note: Bold type indicates statistically significant difference

6.10 The meta-analyses of mean percentage change from baseline indicated that treatment with inclisiran was associated with an approximately 50% reduction in LDL-C compared to placebo. These results were consistent across all trials (ORION 9, 10, 11). The results of the primary analysis were relatively robust, whereas sensitivity analyses using different imputation methods introduced a substantial degree of heterogeneity between trials. Similar results were also estimated for the steady state dosing period (between 90 and 540 days) although there was a substantial degree of heterogeneity between trials.

- 6.11 Additional post hoc subgroup analyses of the co-primary LDL-C outcomes indicated a highly statistically significant treatment interaction ($p < 0.00001$) between subgroups defined by baseline LDL-C levels, with smaller reductions observed in patients with higher baseline levels. The differences in treatment effects between subgroups appeared to be largely driven by changes in the comparator arm. Expert advice provided in the inclisiran submission to NICE suggested that these differences could have been due to varying compliance to background lipid lowering medication (pp99-100, NICE committee papers for ID1647). Additionally, patients with higher LDL-C levels may have been more likely to initiate a new lipid lowering therapy over the course of the trial. The submission noted that similar patterns have also been observed with other PCSK9 inhibitor therapies.
- 6.12 During the evaluation, it was noted that the submission excluded a substantial number of potentially relevant trials from the indirect comparisons against ezetimibe, evolocumab and alirocumab. Additionally, the submission inconsistently pooled results from comparator trials (particularly LDL-C outcomes from the large cardiovascular outcome studies) and excluded comparator treatment arms using moderate-intensity background statins which was poorly justified given that patients in the ORION trials were allowed to use moderate-intensity statins (if that was the maximally tolerated dose). To address these limitations, the results of the indirect analyses were considered alongside the results of published network meta-analyses that compared inclisiran, ezetimibe, evolocumab and alirocumab (Burnett 2022, Huang 2022, Toth 2022). The PSCR reiterated that the submission excluded studies found not be applicable to the proposed listing and/or not exchangeable with the included inclisiran studies. The PSCR noted that Burnett 2022, Huang 2022 and Toth 2022 were excluded from the submission due to inappropriate measurement of change in LDL-C and lack of applicability in terms of background statin therapies. The ESC considered that, although the data provided in the submission was appropriate, it should have also been reflective of the broader pool of data available and of the meta-analyses.
- 6.13 It should be noted that the submission did not provide a comparison between inclisiran and low dose alirocumab. The PBAC has previously considered that alirocumab was less efficacious at the lower strength (75 mg fortnightly) and that non-inferiority of this lower dose had not been established with the higher strength of alirocumab (150 mg fortnightly) nor with evolocumab (paragraph 6.8, alirocumab PSD, March 2020 PBAC meeting).
- 6.14 The submission did not provide any comparative data in statin-intolerant patients which is a significant limitation given the extensive body of evidence supporting the use of both evolocumab and alirocumab in this population. The PSCR stated that 5 to 10% of patients in the ORION trials did not receive a statin as a background therapy due to documented statin intolerance and that the complementary subgroup analyses demonstrated that background statin therapy was not a significant inclisiran treatment effect modifier. Therefore, the efficacy of inclisiran in these patients is not

expected to differ to those receiving background statin therapy. The PSCR also stated that the pooled efficacy and safety of inclisiran in patients with statin intolerance from ORION-10/11 has been published (Wright et al, 2020), which confirmed these results. The ESC noted that this claim was inconsistent with the submission which noted that statin-intolerance was a potential treatment effect modifier, with smaller LDL-C reductions in statin-intolerant patients. The ESC also noted that the body of evidence supporting the use of PCSK9 inhibitor therapies in statin-intolerant populations was far more extensive (GAUSS-2, GAUSS-3, GAUSS-4, ODYSSEY-ALTERNATIVE) than the evidence provided for inclisiran.

- 6.15 Table 5 summarises the studies included in the indirect analysis and the base case analysis for each of the published network meta-analyses.

Table 5: Summary of placebo-controlled studies included in the submission and the base case analysis for each of the published network meta-analyses

Trials	Submission	Burnett 2022	Huang 2022	Toth 2022
Inclisiran versus placebo trials				
ORION 1	x	x	x	✓
ORION 9	✓	x	✓	✓
ORION 10	✓	✓	✓	✓
ORION 11	✓	✓	✓	✓
Ezetimibe versus placebo trials				
ACCENTUATE	✓	x	x	x
EASE	✓	x	x	x
LAPLACE-2	x	✓	✓	✓
ENHANCE	x	x	x	✓
IMPROVE-IT	x	x	x	✓
Ballantyne (2020)	x	✓	x	✓
Masana (2005)	x	x	x	✓
Evolocumab versus placebo trials				
LAPLACE	x	✓	x	✓
LAPLACE-2	✓	✓	✓	✓
BANTING	✓	x	✓	✓
DESCARTES	✓	x	✓	✓
FOURIER	✓	✓	✓	✓
RUTHERFORD-1	✓	x	x	✓
RUTHERFORD-2	✓	x	✓	✓
TESLA	x	x	✓	x
YUKAWA	x	x	x	✓
YUKAWA-2	x	x	✓	✓
BERSON	x	x	✓	✓
GLAGOV	x	x	x	✓
Alirocumab versus placebo trials				
COMBO-I	✓	✓	✓	✓
CHOICE-I	✓	✓	✓	✓
CHOICE-II	✓	x	x	✓
KT	✓	✓	✓	✓
INSULIN-DM	✓	x	✓	✓
LONG-TERM	✓	✓	✓	✓
OUTCOMES	✓	✓	x	x
FH-I	✓	x	✓	✓
FH-II	✓	x	✓	✓
HIGH-FH	✓	x	✓	✓
JAPAN	x	x	✓	✓
NIPPON	x	x	x	✓
McKenny (2012)	x	✓	x	✓
Stein (2012)	x	x	x	✓
Teramoto (2016)	x	x	x	✓

Source: Table 2.36 of the submission; Burnett (2022) publication; Huang (2022) publication; Toth (2022) publication

6.16 The submission acknowledged that there were potential differences between the inclisiran and comparator trials that may limit the exchangeability of outcomes. These differences include patient characteristics (age, gender, background lipid lowering therapy, baseline LDL-C levels) and study characteristics (duration, statistical analyses, and data imputation).

6.17 Table 6 summarises the mean percentage change in LDL-C from baseline for each of the treatments relative to placebo or inclisiran.

Table 6: Summary of results from indirect analyses presented in the submission and the base case analysis for each of the published network meta-analyses

Treatments	Submission	Burnett 2022	Huang 2022	Toth 2022
Mean (95% CI) percentage change from baseline in LDL-C compared to placebo				
Inclisiran	ASCVD MIWM: -50.94 (-53.33, -48.56) ASCVD MMRM: -54.95 (-59.42, -50.48) HeFH MMRM: -48.82 (-54.32, -43.32) Economics ^a : -57.24 (-60.36, -54.13)	-57.49 (-65.34, -49.48)	-50.08 (-54.82, -45.34)	-50.17 (-54.99, -45.35)
Ezetimibe	Clinical: -25.46 (-27.67, -23.26) Economics ^b : -23.71 (-26.73, -20.70)	-24.97 (-31.17, -18.60)	-25.34 (-29.25, -21.43)	-24.49 (-27.48, -21.49)
Evolocumab	ASCVD: -61.05 (-68.48, -53.63) HeFH: -59.05 (-63.12, -54.98) Economics ^c : -57.24 (-60.36, -54.13)	-65.65 (-72.08, -59.37)	-63.41 (-65.59, -61.23)	-64.68 (-67.37, -62.00)
Alirocumab	ASCVD short-term: -54.37 (-60.10, -48.64) ASCVD long-term: -54.02 (-55.59, -52.46) HeFH: -50.85 (-59.81, -41.89)	-58.25 (-62.71, -53.58)	-54.64 (-57.73, -51.55)	75 mg fortnightly: -53.26 (-56.40, -50.13) 150 mg fortnightly: -62.71 (-67.56, -57.87) 300 mg monthly: -51.62 (-59.26, -43.98)
Mean (95% CI) percentage change from baseline in LDL-C compared to inclisiran				
Ezetimibe	Clinical: 25.48 (28.73, 22.23) Economics: 33.53 (37.87, 29.20)	32.48 (42.62, 22.39)	24.75 (18.60, 30.89)	25.69 (20.01, 31.36)
Evolocumab	ASCVD: -6.10 (1.32, -13.52) HeFH: -10.23 (-3.39, -17.07) Economics ^a : 0.00	-8.16 (1.82, -18.49)	-13.33 (-18.54, -8.11)	-14.51 (-20.03, -8.99)
Alirocumab	ASCVD short-term: 0.58 (7.85, -6.69) ASCVD long-term: 0.93 (5.67, -3.81) HeFH: -2.03 (8.48, -12.54)	-0.78 (-8.35, 9.88)	-4.55 (-10.21, 1.10)	75 mg fortnightly: -3.09 (-8.84, 2.66) 150 mg fortnightly: -12.54 (-19.37, -5.71) 300 mg monthly: -1.44 (-10.48, 7.59)

Source: Figure 46; Table 47; Table 66 of the submission; Figure 1; Table 11; Figure 2; Table 10; Attachment 4 of the submission; Burnett (2022) publication; Huang (2022) publication; Toth (2022) publication

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; HeFH, heterozygous familial hypercholesterolaemia; MIWM, multiple imputation washout model; MMRM, mixed effect model for repeated measures

^a ORION 10 trial

^b EASE trial

^c Assumed to be the same as inclisiran

6.18 The mean change in LDL-C from baseline associated with ezetimibe (approximately 25%), evolocumab (approximately 65%) and alirocumab (approximately 50-65% varying by dose) compared to placebo was consistent across all published network meta-analyses. However, the mean change in LDL-C associated with inclisiran compared to placebo was more variable between analyses which appeared to be

primarily due to differences in outcome definition (Burnett used previously unpublished MMRM results at Day 150 while Huang and Toth used primary outcomes as reported from the ORION trials).

- 6.19 Based on the indirect analyses presented in the submission, treatment with inclisiran was associated with a statistically significant reduction in LDL-C levels compared to ezetimibe in patients with ASCVD or ASCVD-risk equivalents.
- 6.20 However, comparisons between inclisiran and evolocumab consistently favoured evolocumab, with the differences reaching statistical significance for patients with HeFH. Comparisons between inclisiran and alirocumab appeared to show similar results with both treatments.
- 6.21 Overall, the submission considered that the differences between inclisiran and evolocumab and alirocumab were small and most did not reach statistical significance. Therefore, the submission argued that the results of the indirect analyses support the claim that inclisiran is non-inferior to evolocumab and alirocumab in terms of lowering LDL-C. However, the lack of a statistically significant difference between treatments may not be sufficient to establish non-inferiority, as the uncertainty associated with the indirect analysis may obscure clinically important differences.
- 6.22 Comparisons between treatments demonstrated that inclisiran was associated with consistently greater reductions in LDL-C compared to ezetimibe but was associated with consistently smaller reductions in LDL-C compared to evolocumab. Treatment with inclisiran appeared to be associated with similar LDL-C reductions to the lower dose strengths of alirocumab (75 mg fortnightly or 300 mg monthly).
- 6.23 The pre-PBAC response stated that the information presented in Table 6 was misleading for the following reasons:
- The analyses do not consider any exchangeability or applicability issues across the included trials;
 - The analyses did not ensure that the methods of imputation to handle missing data were similar across the included trials;
 - The study durations differed; and
 - Toth, unlike Burnett and Huang, analysed the 75 mg dose of alirocumab separately to the 150 mg dose; however, it would have been more appropriate to evaluate the efficacy of the alirocumab treatment algorithm, as patients who do not respond to the 75 mg dose will move to the higher doses.

Comparative harms

- 6.24 Table 7 presents an overall summary of the adverse events reported with inclisiran and placebo treatment in the ORION trials.

Table 7: Summary of adverse events in the inclisiran trials

Adverse event category	ORION 9		ORION 10		ORION 11	
	Inclisiran N = 241 n (%)	Placebo N = 240 n (%)	Inclisiran N = 781 n (%)	Placebo N = 778 n (%)	Inclisiran N = 811 n (%)	Placebo N = 804 n (%)
Any adverse event	185 (76.8%)	172 (71.7%)	574 (73.5%)	582 (74.8%)	671 (82.7%)	655 (81.5%)
Treatment-related adverse event	58 (24.1%)	10 (4.2%)	105 (13.4%)	85 (10.9%)	123 (15.2%)	82 (10.2%)
Serious adverse event	18 (7.5%)	33 (13.8%)	175 (22.4%)	205 (26.3%)	181 (22.3%)	181 (22.5%)
Adverse events leading to discontinuation	3 (1.2%)	0 (0.0%)	19 (2.4%)	17 (2.2%)	23 (2.8%)	18 (2.2%)
Deaths	1 (0.4%)	1 (0.4%)	12 (1.5%)	11 (1.4%)	14 (1.7%)	15 (1.9%)
Adverse events of special interest						
Injection site reaction	41 (17.0%)	4 (1.7%)	47 (6.0%)	15 (1.9%)	62 (7.6%)	14 (1.7%)
Hepatic events	5 (2.1%)	2 (0.8%)	23 (2.9%)	31 (4.0%)	42 (5.2%)	43 (5.3%)
Renal events	3 (0.4%)	3 (0.4%)	32 (4.1%)	35 (4.5%)	27 (3.3%)	22 (2.7%)
Cardiac events	14 (5.8%)	20 (8.3%)	109 (14.0%)	135 (17.4%)	138 (17.0%)	145 (18.0%)
New/worsening diabetes	18 (7.5%)	13 (5.4%)	148 (19.0%)	137 (17.6%)	124 (15.3%)	130 (16.2%)
Hypersensitivity	22 (9.1%)	16 (6.7%)	61 (7.8%)	72 (9.3%)	53 (6.5%)	49 (6.1%)
Neurologic or neurocognitive events	2 (0.8%)	6 (2.5%)	28 (3.6%)	30 (3.9%)	23 (2.8%)	33 (4.1%)
Ophthalmological events	3 (1.2%)	2 (0.8%)	11 (1.4%)	8 (1.0%)	13 (1.6%)	11 (1.4%)

Source: Table 33 of the submission; Section 12.5 of the ORION-9 trial report; Section 12.5 of the ORION-10 trial report; Section 12.5 of the ORION-11 trial report

- 6.25 The most frequently occurring adverse events ($\geq 5\%$ of subjects in any arm) in the inclisiran trials were nasopharyngitis, influenza, upper respiratory tract infection, back pain, injection site reactions, hypertension, bronchitis, diabetes, dyspnoea, arthralgia, and osteoarthritis.
- 6.26 Treatment with inclisiran was associated with an increased incidence of treatment-related adverse events (primarily mild-to-moderate injection site reactions) compared to placebo. Consistent with the exploratory cardiovascular outcomes, treatment with inclisiran also appeared to be associated with a reduction in the incidence of cardiac events compared to placebo. The incidence of other adverse events was generally similar between treatment arms.
- 6.27 The submission provided additional data on potential safety concerns with inclisiran based on a Periodic Safety Update Report (January 2022 to June 2022). No new safety concerns were identified in the report. There were no important identified risks or important potential risks associated with inclisiran treatment. The report noted that there was missing information on long term safety, use in pregnancy and breastfeeding and use in severe hepatic impairment. The PSCR stated that long-term safety data from the 5-year ORION 3 open label study which indicated the incidence of treatment emergent adverse events possible related to inclisiran was 1% (3/284) in the inclisiran-only arm and 1% (1/87) in the switching arm.

- 6.28 The submission did not present any comparisons of safety between inclisiran and nominated comparators but claimed that all of the therapies are considered safe and well-tolerated.

Benefits/harms

- 6.29 On the basis of the indirect evidence presented in the submission, the comparison of inclisiran and ezetimibe resulted in:
- Approximately an additional 25% reduction in LDL-C levels compared to baseline over the trial durations (between 6 weeks and 18 months). The submission did not nominate a minimal clinically important difference in LDL-C levels.
 - No safety data were presented to allow a comparative assessment of harms.
- 6.30 An assessment of benefits and harms was not conducted for comparisons against PCSK9 inhibitor therapies (evolocumab, alirocumab) given the claim of non-inferiority.

Clinical claim

- 6.31 The submission described inclisiran as superior to ezetimibe in terms of comparative effectiveness and non-inferior in terms of safety. The ESC considered that this claim was reasonable in terms of comparative effectiveness but uncertain in terms of safety given the lack of comparative and long-term safety data.
- 6.32 The submission described inclisiran as non-inferior compared to PCSK9 inhibitors (evolocumab and alirocumab) in terms of comparative effectiveness and safety. In terms of comparative effectiveness, the ESC considered that although inclisiran was broadly comparable to the PCSK9 inhibitor therapies, the claim of non-inferiority was uncertain based on the evidence presented, noting that inclisiran was possibly inferior to evolocumab and high dose alirocumab with statistically significantly worse results compared to evolocumab in HeFH. In terms of safety, the ESC considered whilst inclisiran appears to have comparable safety to PCSK9 inhibitors and is reasonably well-tolerated, the claim was uncertain given the lack of comparative and long-term safety data.
- 6.33 The ESC considered that the following issues should be considered:
- The robustness of limiting data to a highly selective evidence base (which was still poorly matched) rather than a broader comprehensive assessment of data for each treatment.
 - The appropriateness of claiming non-inferiority to PCSK9 inhibitor therapies based on a lack of statistically significant difference between therapies in the indirect comparisons particularly given that results consistently favoured evolocumab over inclisiran and the magnitude of difference between therapies may be clinically important.
 - The lack of comparative data between inclisiran, ezetimibe and PCSK9 inhibitors in patients with statin-intolerance.

- 6.34 The PBAC considered that the claim of non-inferior comparative effectiveness to the PCSK9 inhibitors was uncertain.
- 6.35 The PBAC considered that the claim of non-inferior comparative safety to the PCSK9 inhibitors was uncertain, though likely comparable.

Economic analysis

- 6.36 The submission presented both a modelled economic evaluation of inclisiran compared to ezetimibe for the second-line treatment of hypercholesterolemia in patients with atherosclerotic cardiovascular disease and a CMA between inclisiran and PCSK9 inhibitor therapies in the subsequent line setting.

Cost effectiveness analysis of inclisiran compared to ezetimibe (followed by PCSK9 inhibitor therapies, if required)

- 6.37 The economic evaluation was based on an indirect comparison of LDL-C outcomes from the ORION-10 and EASE trials with additional modelled data. The economic evaluation was presented as a cost-effectiveness/cost-utility analysis. The ESC noted the trials selected for inclusion in the model and the assumption of the same treatment effect as inclisiran for PCSK9 inhibitors favoured inclisiran.

Table 8: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-effectiveness/cost-utility analysis
Outcomes	Cardiovascular events, life years, quality adjusted life years
Time horizon	Lifetime (maximum 60 years)
Methods used to generate results	Markov state-transition cohort models (with half cycle correction) based on multiple simulations of individual patient data (1,051 patient cohorts)
Treatments	Inclisiran; ezetimibe (followed by PCSK9 therapy if required)
Health states	9 health states based on treatment status (second-line, subsequent-line, discontinued) and history of cardiovascular events (pre-event, post-myocardial infarction, post-stroke). The model also includes two death states; cardiovascular death and background mortality
Cycle length	1 year
Patient characteristics and circumstances of use	Age, gender, smoking history, LDL/HDL/TC levels, history of coronary artery disease/cerebrovascular disease/peripheral arterial disease, history of diabetes and baseline statin use were estimated based on individual patient data from the ORION clinical trial program. Mean hs-CRP level, mean systolic blood pressure, mean eGFR and the proportion of patients with an aortic aneurysm were based on aggregate data from the SMART derivation cohort (Dorresteijn 2013). The average time since diagnosis was based on aggregate data from the Code Red report (Carrington 2020). The submission assumed perfect compliance to background statin therapy for all patients. The submission estimated treatment persistence for inclisiran, ezetimibe and PCSK9 inhibitor therapies based on treatment discontinuations from the inclisiran treatment arm in the subgroup of patients with atherosclerotic cardiovascular disease in the ORION 10/11 trials. The submission assumed that all patients were perfectly adherent to these therapies while on treatment. The submission assumed that both inclisiran and PCSK9 inhibitor therapies required administration by a medical professional. The ESC noted that the PCSK9 inhibitor therapies did not require administration by a medical professional, and that correction of this error substantially increased the base case ICER.

Public Summary Document - March 2023 PBAC Meeting with May 2023 Addendum

Component	Description
Transition probabilities	The annual risk of major cardiovascular events was estimated based on synthesised patient characteristics using the SMART risk equation (Dorresteijn 2013). The underlying risk was updated over time based on age and number of vascular beds affected. The distribution of myocardial infarction, stroke and cardiovascular death events was estimated based on Australian REACH registry data (Steg 2007). Treatment effects were estimated using a multi-step approach transforming LDL-C reductions for ezetimibe (based on the EASE trial) and inclisiran/PCSK9 inhibitor therapies (based on the ORION-10 trial, assuming equivalent efficacy) into cardiovascular risk reductions using the CTTC meta-analysis (CTTC 2019, Collins 2016). The submission assumed a time delay of 2-4 years in achieving maximum cardiovascular risk reductions. The submission assumed that patients in the comparator arm who failed to achieve an LDL-C < 1.8 mmol/L after one year of ezetimibe treatment will switch to PCSK9 inhibitor therapies. The submission assumed that treatment effects were maintained while patients remained on therapy. The annual risk of non-cardiovascular death was estimated based on Australian life tables adjusted to exclude death from cardiovascular causes.
Utility values	Health state utility values and cardiovascular event disutility values were based EQ-5D-3L data from the OUTCOMES trial (Bhatt 2020).
Costs	Inclisiran drug costs were estimated based on the proposed 'placeholder' effective price. Atorvastatin (proxy for all statin therapies), ezetimibe and evolocumab (proxy for all PCSK9 inhibitor therapies) drug costs were estimated based on published PBS prices. Drug administration costs were estimated for inclisiran and PCSK9 inhibitor therapies based on MBS costs for a GP visit. The event and health state costs of non-fatal cardiovascular events were estimated from various published sources (National Heart Foundation ACS cost report 2018, Tan Tanny 2013, Gloede 2014, AIHW stroke report 2013). Costs estimated in the submission were inflated to 2022 values using the health sub-category of the consumer price index. The cost of cardiovascular death was estimated based on AR-DRG cost weights assuming all patients would be hospitalised.
Discount rate	5% for costs and outcomes
Software package	TreeAge Pro Healthcare 2022 with Microsoft Excel used to average results across all simulated cohorts

Source: Table 60 of the submission

Abbreviations: CTTC, Cholesterol Treatment Trialists Collaboration; LDL-C, low density lipoprotein cholesterol

- 6.38 All patients begin the model in the pre-event health state and are allocated to either inclisiran or ezetimibe. During each annual cycle, patients could remain in their current health state or experience a non-fatal myocardial infarction and/or non-fatal stroke or cardiovascular death or non-cardiovascular death. Patients experiencing multiple non-fatal events accrue the acute costs and consequences of each event and have ongoing chronic costs and consequences based on the most severe event (with stroke worse than myocardial infarction).
- 6.39 During each cycle of the model, patients in both treatment arms could discontinue treatment (i.e. have no LDL-C lowering treatment effects beyond background therapy). Additionally, patients in the comparator arm were assessed after the initial year of treatment. Patients who achieved an LDL-C level < 1.8 mmol/L continued to

receive ezetimibe treatment and never become eligible for PCSK9 therapy. Patients who failed to achieve the LDL-C target were assumed to discontinue ezetimibe treatment and switch to PCSK9 inhibitor therapy. The ESC noted that the submission did not justify the assumption that PCSK9 inhibitor therapies would replace, rather than be used in addition to ezetimibe.

6.40 Key drivers of the economic model are summarised in Table 9.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Inclisiran LDL treatment effect	The submission estimated LDL-C treatment effects for inclisiran based on the ORION-10 trial. The submission claimed that this was the most applicable study from the ORION clinical trial program as all patients had atherosclerotic cardiovascular disease. The estimate used in the submission was based on a sensitivity analysis using a mixed effect model for repeated measures (MMRM) to handle missing data. The submission did not adequately justify limiting the treatment efficacy data to the ORION-10 trial given that the ORION-9/10/11 trials are used to inform patient characteristics and ORION 10/11 trials are used to inform treatment discontinuations. The PSCR noted that the meta-analysed estimate from the ORION 10/11 trials resulted in a very small difference in magnitude -54.95%, as compared to -57.24% as used in the model. The PSCR also stated that the ORION-10 trial was used as it was the most applicable inclisiran trial to the target PBS population (patients with prior ASCVD and LDL-C ≥ 1.8 mmol/L despite maximum tolerated statin therapy). The ESC noted that the ICER was sensitive to the use of treatment efficacy data from the ORION 10/11 trials (base case increased by 33%). Additionally, the estimated treatment efficacy for ezetimibe used in the model was based on the EASE trial, which included a mixed population of patients with atherosclerotic cardiovascular disease or risk equivalents and therefore the exclusion of the ORION-11 trial (which also included a mixed population) does not appear to be reasonable.	High, favours inclisiran
Ezetimibe LDL-C treatment effect	The submission estimated LDL-C treatment effects for ezetimibe based on the EASE trial. It was unclear whether the efficacy estimates used in the model are a robust representation of ezetimibe treatment effects given the exclusion of a substantial number of potentially relevant trials and treatment arms from consideration in the clinical analyses. The ESC noted that the ICER was sensitive to the use of treatment efficacy data from the EASE/ACCENTUATE trials (base case increased by 91%).	High, favours inclisiran
PCSK9 LDL treatment effect	The submission assumed that LDL-C treatment effects for PCSK9 inhibitor therapies were equivalent to inclisiran. This assumption may not be reasonable given that clinical data consistently showed that treatment with evolocumab was associated with greater reductions in LDL-C cholesterol compared to inclisiran. Additionally, the PBAC has previously noted that not all PCSK9 inhibitor therapies are equivalent, with low dose alirocumab (75 mg fortnightly, 150 mg monthly) potentially being inferior to other PCSK9 inhibitor therapies (paragraph 6.8, alirocumab PSD, March 2020 PBAC meeting). The ESC noted that the ICER was sensitive to the use of separate efficacy estimates (i.e. not assuming the same efficacy for inclisiran and evolocumab) based on Burnett 2022 (base case increased by 203%; base case dominated if based on Huang 2022 NMA or Toth 2022 NMA).	High, favours inclisiran

Public Summary Document - March 2023 PBAC Meeting with May 2023 Addendum

Description	Method/Value	Impact
Treatment discontinuations	The submission estimated treatment discontinuations based on a post hoc analysis of pooled data from the subgroup of patients with atherosclerotic cardiovascular disease who were treated with inclisiran in the ORION 10/11 trials. The reported discontinuation rate with inclisiran treatment in a highly regulated clinical trial setting over a duration of 18 months may not be representative of discontinuations in clinical practice over the longer term. The submission assumed that all therapies (inclisiran, ezetimibe, evolocumab) have the same discontinuation rate. However, it remains clinically plausible that there may be important differences in discontinuations between therapies given the differences in both the frequency and mode of administration.	High, unclear direction
Treatment switching	The submission assumed that all patients in the comparator arm would initially receive one year of treatment with ezetimibe. After one year, patients who achieved an LDL-C target of < 1.8 mmol/L were assumed to remain on ezetimibe and never become eligible for PCSK9 therapy. Patients who failed to achieve the LDL-C target after one year of ezetimibe treatment were assumed to discontinue therapy and switch to PCSK9 inhibitor therapies.	High, favours inclisiran
Evolocumab script duration	The submission assumed that each script of evolocumab 420 mg would last 28 days, which appeared to be based on the script coverage of the evolocumab 140 mg dose strength (2 injections per script, one injection per fortnight with 13.04 scripts per year). Based on the product information, evolocumab 420 mg is administered as a monthly dose and therefore there should be approximately 12 scripts per year. The assumption that patients using evolocumab 420 mg would require 13.04 scripts per year was also inconsistent with the CMA presented in the submission which assumed that patients would require 12 scripts per year. The PSCR acknowledged that the 420 mg dose was inconsistently estimated between the cost effectiveness analysis and the CMA.	High, favours inclisiran
Evolocumab administration costs	The submission assumed that a medical professional would be required to administer each evolocumab injection. The assumption that evolocumab requires administration by a medical professional was also inconsistent with the CMA presented in the submission which assumed that all patients would self-administer PCSK9 inhibitor therapies. The PSCR acknowledged that the administration costs for the PCSK9 inhibitor therapies was inappropriate and should be excluded. Analyses presented in the commentary indicate that exclusion of administration costs increases the ICER from \$ [REDACTED] ¹ per QALY gained in the base case to \$ [REDACTED] ² per QALY gained.	High, favours inclisiran

Source: Constructed during the evaluation

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$75,000 to < \$95,000

- 6.41 The treatment switching rule included in the economic analysis for ezetimibe patients resulted in two distinct modelled patient populations based on whether patients were eligible or ineligible for PCSK9 therapy.
- 6.42 Treatment with inclisiran was associated with substantial reductions in the risks of myocardial infarction, stroke and cardiovascular death compared to ezetimibe in patients who were ineligible for PCSK9 therapy (as they achieved target LDL-C levels with ezetimibe and therefore did not qualify for PCSK9 therapy). The improved

cardiovascular outcomes were due to patients being able to push their LDL-C levels further below treatment targets with inclisiran compared to ezetimibe.

- 6.43 Treatment with inclisiran was associated with a marginally higher incidence of myocardial infarction, stroke and cardiovascular death compared to the comparator arm in patients who were eligible for PCSK9 therapy (patients who failed to achieve target LDL-C levels after one year of treatment with ezetimibe and switched to evolocumab). The small difference in outcomes was due to a difference in treatment discontinuations. Patients discontinuing ezetimibe in the first year of treatment were allowed to start treatment with evolocumab in the second year while patients in the inclisiran arm were never allowed to restart therapy after treatment discontinuation.
- 6.44 The results of the modelled economic evaluation, based on published prices, are summarised in Table 10.

Table 10: Results of the modelled economic evaluation

Type of resource item	Inclisiran	Comparator	Incremental difference
Overall modelled population			
Costs	\$█	\$48,729	█
Quality adjusted life years	9.4002	9.3647	0.0355
Incremental cost per quality adjusted life year gained			█¹
Patients who are ineligible for PCSK9 inhibitor therapy (i.e. have achieved LDL-C ≤ 1.8 mmol/L and remain on ezetimibe without a PCSK9 inhibitor) (441 of the 1,051 modelled cohorts)			
Costs	\$█	\$18,293	█
Quality adjusted life years	9.2887	9.1977	0.0911
Incremental cost per quality adjusted life year gained			█²
Patients who are eligible for PCSK9 inhibitor therapy (i.e. LDL-C remains > 1.8 mmol/L with 12 months ezetimibe treatment and 100% switch to PCSK9 inhibitor) (610 of the 1,051 modelled cohorts)			
Costs	\$█	\$70,732	-\$█
Quality adjusted life years	9.4807	9.4855	-0.0047
Incremental saving per quality adjusted life year foregone			█³

Source: Table 82 of the submission; additional analyses conducted during the evaluation based on the 'Section 3 model 24.10.2022 clean' TreeAge file

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$255,000 to < \$355,000

³ > \$1,055,000

- 6.45 Based on the overall population, treatment with inclisiran was associated with an incremental cost per QALY gained of \$35,000 to < \$45,000 compared to ezetimibe and PCSK9 inhibitor therapies for the treatment of hypercholesterolaemia. The ESC noted that removal of the administration costs associated with the PCSK9 inhibitor therapies would result in a revised base case ICER of \$75,000 to < \$95,000 per QALY gained (see Table 11).
- 6.46 The ESC also noted the use of inclisiran was not cost-effective in patients who would have otherwise achieved target LDL-C levels with ezetimibe alone (i.e. PCSK9 ineligible patients) as the ICER in this group was \$255,000 to < \$355,000 per QALY gained. In addition, the ESC noted that although the use of inclisiran in patients who would have switched to PCSK9 inhibitor therapies (i.e. PCSK9 eligible patients) could

potentially result in cost savings, it would also likely result in less clinical benefits (incremental QALYs = -0.0047). The ESC considered the disaggregated ICERs showed the base case ICER was misleading as it was strongly driven by the patients becoming eligible for subsequent PCSK9 inhibitor therapies.

- 6.47 The PBAC has previously considered than an ICER of less than \$25,000 to < \$35,000 per QALY gained would be required for a hypercholesterolemia treatment to be considered cost-effective in the secondary prevention setting when the magnitude of the mortality benefit was unknown (para 7.11, evolocumab PSD, July 2022 PBAC meeting).
- 6.48 For every 1,000 patients treated with inclisiran versus comparator therapies and followed up over their lifetime, the economic evaluation (undiscounted) estimated that there would be:
- Decreased incidence of myocardial infarction (9 fewer events), stroke (7 fewer events) and cardiovascular death (7 fewer events) with a small increase in survival (average 30 days per patient).
 - Additional drug and administration costs of \$1.5 million but decreased cardiovascular event and disease management costs of \$0.9 million.
- 6.49 The results of the sensitivity analyses indicated that the model was highly sensitive, particularly to the discount rate, time horizon, circumstances of use (differential discontinuations between treatments, evolocumab uptake rate and use of concomitant ezetimibe and evolocumab treatment), estimated treatment effects (mean percentage change in LDL-C) as well as drug and administration costs (evolocumab price, script duration and administration costs). The ESC noted that the multivariate sensitivity analysis which made the following changes to the evolocumab component (i) used the updated DPMQ, (ii) applied 12 prescriptions per year, and (iii) removed the administration costs, increased the ICER by over 1,000%.

Table 11: Results of sensitivity analyses

Analyses	Incremental cost (\$)	Incremental QALY	ICER (\$)	Change from base case ICER
Base case		0.0355	1	-
Discount rate (base case: 5% for benefits and costs)				
3.5% discount rate		0.0437	2	-30%
0% discount rate		0.0757	3	-82%
Time horizon (base case: lifetime)				
10 years		0.0116	4	+315%
20 years		0.0278	6	+38%
Circumstances of use (base case: discontinuation rate for all treatments based on inclisiran discontinuation from the ORION 10/11 subgroup with ASCVD; assumed 100% annual uptake of evolocumab in PCSK9 eligible patients; assumed all patients discontinued ezetimibe after switching to evolocumab)				
No discontinuation from any treatment		0.0554	1	-6%
Discontinuation rate halved for all treatments		0.0442	1	-3%
Discontinuation rate doubled for all treatments		0.0229	13	+6%
Discontinuation rate halved for inclisiran only		0.0775	5	+61%

Public Summary Document - March 2023 PBAC Meeting with May 2023 Addendum

Analyses	Incremental cost (\$)	Incremental QALY	ICER (\$)	Change from base case ICER
Base case		0.0355	█¹	-
Discontinuation rate doubled for inclisiran only		-0.0266	█⁴	NE
Discontinuation rate halved for comparator therapies only		0.0023	Dominant	NE
Discontinuation rate doubled for comparator therapies only		0.0849	█⁶	+89%
75% annual uptake of evolocumab in PCSK9 eligible patients		0.0379	█⁵	+61%
50% annual uptake of evolocumab in PCSK9 eligible patients		0.0430	█⁷	+149%
25% annual uptake of evolocumab in PCSK9 eligible patients		0.0573	█⁴	+278%
Assume all patients switching to evolocumab continue ezetimibe with drug costs and 100% of ezetimibe efficacy		-0.0156	Dominated	NE
Assume all patients switching to evolocumab continue ezetimibe with drug costs and 75% of ezetimibe efficacy		-0.0034	Dominated	NE
Assume all patients switching to evolocumab continue ezetimibe with drug costs and 50% of ezetimibe efficacy		0.0092	█⁵	+30%
Assume all patients switching to evolocumab continue ezetimibe with drug costs and 25% of ezetimibe efficacy		0.0220	█⁸	-53%
Mean percentage change in LDL-C (base case: based on ORION 10 MMRM results for inclisiran and EASE results for ezetimibe; assumed evolocumab has same efficacy as inclisiran)				
Inclisiran based on ORION 10/11 MIWM results		0.0285	█⁵	+33%
Ezetimibe based on EASE/ACCENTUATE results ^a		0.0352	█⁶	+91%
Inclisiran based on ORION 10/11 MIWM results and ezetimibe based on EASE/ACCENTUATE results ^a		0.0277	█⁷	+151%
All treatments have separate efficacy estimates (i.e. does not assume the same efficacy for inclisiran and evolocumab) based on Burnett 2022 NMA		0.0171	█⁹	+203%
All treatments have separate efficacy estimates (i.e. does not assume the same efficacy for inclisiran and evolocumab) based on Huang 2022 NMA		-0.0031	Dominated	NE
All treatments have separate efficacy estimates (i.e. does not assume the same efficacy for inclisiran and evolocumab) based on Toth 2022 NMA		-0.0062	Dominated	NE
Drug and administration costs (base case: inclisiran costs based on placeholder effective DPMQ with 3 scripts first year and 2 scripts subsequent years, ezetimibe costs based on single agent DPMQ with 12.175 scripts per year, evolocumab costs based on published DPMQ for 420 mg dose with 13.04 scripts per year; statin costs based on atorvastatin DPMQ with 12.175 scripts per year; assumed inclisiran and PCSK9 inhibitor therapies required administration by a medical professional)				
Replace statin and ezetimibe in comparator arm with ezetimibe/statin FDC		0.0355	█⁵	+33%

Analyses	Incremental cost (\$)	Incremental QALY	ICER (\$)	Change from base case ICER
Base case		0.0355	■ ¹	-
Use updated published DPMQ for evolocumab [changed 1 December]		0.0355	■ ¹⁰	+567%
Use 12 scripts per year for evolocumab 420 mg dose (same as CMA)		0.0355	■ ¹¹	+158%
Assume no administration costs for evolocumab (same as CMA)		0.0355	■ ⁶	+70%
Use updated evolocumab costs, 12 scripts per year and no administration costs		0.0355	■ ¹²	+1,235%

Source: Table 83 of the submission; additional analyses conducted during the evaluation based on the 'Section 3 model 24.10.2022 clean' TreeAge file

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CMA, cost minimisation analysis; CTTC, Cholesterol Treatment Trialists Collaboration; DPMQ, dispensed price per maximum quantity; FDC, fixed dose combination; ICER, incremental cost effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; MIWM, multiple imputation washout model; MMRM, mixed effect model for repeated measures; NE, not estimable; NMA, network meta-analyses; QALY, quality-adjusted life year

^a There was an error in the calculation of this sensitivity analysis in the submission which used an LDL-C reduction of -25.93% for ezetimibe instead of -25.46%. This error was not corrected during the evaluation.

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$25,000 to < \$35,000

³ \$5,000 to < \$15,000

⁴ \$155,000 to < \$255,000

⁵ \$55,000 to < \$75,000

⁶ \$75,000 to < \$95,000

⁷ \$95,000 to < \$115,000

⁸ \$15,000 to < \$25,000

⁹ \$135,000 to < \$155,000

¹⁰ \$255,000 to < \$355,000

¹¹ \$115,000 to < \$135,000

¹² \$555,000 to < \$655,000

¹³ \$45,000 to < \$55,000

CMA of inclisiran compared to PCSK9 inhibitor therapies

- 6.50 The submission also presented a supportive CMA of inclisiran compared to PCSK9 inhibitor therapies in the subsequent-line setting. The ESC considered that a revised CMA would be reasonable if inclisiran was positioned as an alternative to the PCSK9 inhibitor therapies.
- 6.51 The CMA was presented on the basis that 284 mg inclisiran administered at month 0, at 3 months and then every 6 months is equivalent to evolocumab 140 mg once fortnightly or 420 mg once monthly (the PSKR acknowledged that the administration of the 420 mg dose in the CMA (monthly) differed to that applied in the cost effectiveness analysis (every four weeks)) based on the submission's claim of non-inferior efficacy and safety between treatments. The ESC considered that this claim may not be appropriate as the clinical data consistently showed that treatment with evolocumab was associated with greater reductions in LDL-C compared to inclisiran.
- 6.52 The ESC also noted that the submission did not estimate equi-effective dosing between inclisiran and alirocumab. This was not appropriate as the PBAC has previously considered that alirocumab was less efficacious at the lower strength (75 mg fortnightly) and that non-inferiority had not been established with the higher strength of alirocumab (150 mg fortnightly) nor with evolocumab (paragraph 6.8, alirocumab PSD, March 2020 PBAC meeting). The submission did not provide an indirect comparison of inclisiran versus low dose alirocumab, however published network meta-analyses suggest similar LDL-C reductions between these two

treatment options. The PSCR stated that the conclusion of non-inferiority of inclisiran relative to alirocumab was based on the overall alirocumab dosing algorithm. Further, the PSCR stated that the comparison between inclisiran and alirocumab 75 mg was confounded by the measurement period for the primary outcomes in the ORION studies (baseline to Day 510) relative to the alirocumab 75 mg dose (which is from the end of the 12-week (84 day) titration phase in which non-responders were up-titrated to 150 mg). The ESC noted the PBAC did not previously accept the overall alirocumab dosing algorithm in its March 2020 recommendation, and it was considered that the equi-effective doses should be adjusted to reflect the ITC with low dose alirocumab.

6.53 The submission did not include any differences in compliance between treatments despite the differences in frequency of administration for inclisiran (two initial doses at Day 1 and Month 3 and then dosed every 6 months, all requiring administration by a health professional) and PCSK9 inhibitor therapies (fortnightly or monthly dosing, self-administered). This may be reasonable as there are currently no clinical data to support a compliance advantage with inclisiran compared to other PCSK9 inhibitor therapies. Additionally, there are no comparative data on the impact of inclisiran and PCSK9 inhibitor therapies on compliance to background oral hypercholesterolaemia treatments. However, it remains clinically plausible that there may be important differences in compliance between therapies.

6.54 The results of the CMA, based on published prices, are summarised in Table 12.

Table 12: Results of the CMA

Evolocumab	140 mg once fortnightly	420 mg once monthly
Cost per dose (published AEMP)	\$206.49	\$447.75
Dose duration	2 weeks	1 month
Total doses (over 27 months)	58.7	27.0
Total medicine cost 27 months	\$12,121.15	\$12,089.25
Total administration cost	\$0	\$0
Total drug + administration costs	\$12,121.15	\$12,089.25
PBS usage (evolocumab)	84.6%	15.4%
Weighted average cost of evolocumab	\$12,116.23	
Weighted average cost of evolocumab using December 2022 schedule prices (see para 6.56)	\$8,594.55	
Inclisiran	284 mg (at 0 months, 3 months and then every 6 months)	
Total doses (over 27 months)	5	
Total drug + administration costs	\$12,116.23	
Total administration costs	\$91.00 (= 5 x \$18.20; MBS item 3)	
Total drug costs	\$12,025.23 (= \$12,116.23 - \$91.00)	
Effective AEMP	\$2,405.05 (= \$12,025.23 / 5)	
Effective DPMQ	\$2,566.33	

Source: Table 86; Table 87 of the submission.

Abbreviations: AEMP, approved ex-manufacturer price; DPMQ, dispensed price for maximum quantity (includes mark-ups and dispensing fees)

Note: A special pricing arrangement exists for evolocumab. A special pricing arrangement is requested for listing inclisiran on the PBS, to be discussed with the Pricing Section following PBAC recommendation.

- 6.55 Based on a CMA, the submission estimated a cost minimised price for inclisiran in the subsequent line treatment setting of \$2,566.33 (DPMQ) per script. The cost-minimised price of inclisiran in the subsequent-line setting was substantially higher than the proposed 'placeholder' effective price for inclisiran in the second-line treatment setting (DPMQ \$█ per script).
- 6.56 The CMA was calculated based on the published AEMPs for the evolocumab 140 mg and 420 mg dose strengths using the June 2022 PBS Schedule. Since the preparation of the submission, the published price of evolocumab decreased substantially from the June 2022 Schedule (AEMP \$206.49 per 140 mg fortnightly dose or \$447.75 per 420 mg monthly dose) to the December 2022 Schedule (AEMP \$146.50 per 140 mg fortnightly dose or \$317.30 per 420 mg monthly dose). The submission also acknowledged that evolocumab is subject to a special pricing arrangement and therefore the published price is not reflective of the effective price subsidised under the PBS.

Drug cost/patient/year

Table 13: Drug cost per patient for inclisiran

	ORION 9, 10 and 11	CEA	CMA	Financials
Cost per script	-	'Placeholder' effective DPMQ \$█	Cost-minimised DPMQ \$2,566.33	Published DPMQ \$2,847.78
Scripts	-	Initial year: 3 ^a Subsequent year: 2 ^a	Initial year: 3 ^a Subsequent year: 2 ^a	Initial year: 2.55 ^b Subsequent year: 1.7 ^b
Cost per year	-	Initial year: \$█ Subsequent year: \$█	Initial year: \$7,698.99 Subsequent year: \$5,132.66	Initial year: \$7,261.84 Subsequent year: \$4,841.23
Year 1 persistence	92.3%-97.1% patients persistent at 18 months	96.8% ^c	100% ^d	100% ^e
Year 2 persistence		93.7% ^c	100% ^d	92.3% ^f
Year 3 persistence		90.7% ^c	-	85.2% ^f
Year 4 persistence		87.8% ^c	-	78.6% ^f
Year 5 persistence		85.0% ^c	-	72.6% ^f
Year 6 persistence		82.3% ^c	-	67.0% ^f

Source: constructed during the evaluation

Abbreviations: CEA, cost-effectiveness analysis; CMA, cost-minimisation analysis

^a Assuming 100% adherence

^b Adjusted for 85% compliance (including adherence and persistence)

^c 96.8% fixed yearly persistence

^d 100% persistence over the selected time horizon of 27 months (to account for loading doses in the first year and maintenance doses in the subsequent year)

^e Assumed

^f 92.3% fixed yearly persistence, applied after Year 1 of the model

Note: The costs per year presented in the table do not include persistence estimates

- 6.57 In the cost-effectiveness analysis, the estimated drug cost for comparator therapies per patient per year was \$256 in the first year (based on ezetimibe single agent DPMQ \$21.04 x 12.175 scripts per year) and either \$256 per year for patients remaining on ezetimibe or \$6,687 per year for patients switching to evolocumab in subsequent years (based on evolocumab 420 mg published DPMQ \$512.63 x 13.04 scripts per year). The price of PCSK9 therapy used in the submission was not reflective of current

effective prices and script duration used for PCSK9 inhibitor therapies was not consistent with item code used to estimate the price.

- 6.58 In the CMA, the estimated drug cost per patient per year for evolocumab was \$6,151 (based on evolocumab 420 mg published DPMQ \$512.63 x 12 scripts per year) or \$6,175 (based on evolocumab 140 mg published DPMQ \$473.38 x 13.04 scripts per year). The price of PCSK9 therapy used in the submission was not reflective of current effective prices, however, the script durations used were consistent with item codes used to estimate prices.
- 6.59 In the financial estimates, the estimated drug cost for substituted ezetimibe per patient per year was \$236 (based on ezetimibe single agent and ezetimibe/statin combination therapies, weighted by PBS utilisation, DPMQ \$22.85 x 12.175 scripts per year x 85% compliance). The estimated drug cost per patient per year for avoided use of subsequent-line PCSK9 inhibitor therapies was \$5,228 (based on evolocumab 420 mg published DPMQ \$512.63 x 12 scripts per year x 85% compliance), \$10,461 (based on evolocumab 140 mg published DPMQ \$473.38 x 26 scripts per year x 85% compliance), \$11,012 (based on alirocumab 75 mg published DPMQ \$498.31 x 26 scripts per year x 85% compliance) or \$5,082 (based on alirocumab 150 mg published DPMQ \$498.31 x 12 scripts per year x 85% compliance). The submission also assumed 94.7% yearly persistence to PCSK9 inhibitor therapies. The prices of PCSK9 inhibitor therapies used in the submission were not reflective of current effective prices and there were errors in script durations used for evolocumab 140 mg, alirocumab 75 mg and alirocumab 150 mg which were not consistent with item codes used to estimate prices.

Estimated PBS usage & financial implications

- 6.60 This submission was considered by DUSC. The submission used a market-share/epidemiological approach to estimate the utilisation and financial impacts associated with the PBS/RPBS listing of inclisiran for the treatment of patients with hypercholesterolaemia and atherosclerotic cardiovascular disease who have additional cardiovascular risk factors and who are unable to achieve target lipid thresholds with statins alone or who are intolerant to statins.
- 6.61 There were no estimates presented of utilisation and financial impact for the third line setting of inclisiran as an alternative to the PCSK9 inhibitors.
- 6.62 The total size of the population eligible for inclisiran treatment was determined based on two populations:
- Patients who would otherwise be treated with ezetimibe. In this population, inclisiran would either replace ezetimibe or be used in addition to ezetimibe.
 - Patients who would otherwise be treated with statin alone. The submission acknowledged there may be patients who are eligible for ezetimibe but who are not receiving treatment with ezetimibe. The submission claimed that some of

these patients may use inclisiran in addition to a statin given inclisiran has a lower dosing frequency and different mode of administration compared to ezetimibe.

- 6.63 The submission requested a grandfathering restriction to accommodate patients participating in the Australian VICTORION-ASCERTAIN Phase IV trial (expected commencement in 2023; approximately 500 to < 5,000 patients) and patient familiarisation program (expected commencement in 2023; approximately 500 to < 5,000 patients), some of whom would meet proposed eligibility criteria for inclisiran. The submission stated that grandfathered patients have not been estimated separately in the model but are captured implicitly through the estimated prevalent population.
- 6.64 The submission did not estimate the financial impact of inclisiran if used only as a subsequent-line alternative to PCSK9 inhibitors.
- 6.65 The evaluation of the financial estimates of the submission was hindered due to poor documentation of the 10% PBS sample analyses used to determine the size of the eligible populations who are on ezetimibe (with or without a statin) or a statin alone. The DUSC noted that estimates from these analyses could not be validated during the evaluation as only summary results were presented, with no description of methodology used to obtain patient estimates from script data (e.g. rules applied including look-back periods, treatment discontinuations/switching). In addition, numerous significant errors were identified in the calculations during evaluation of the submission.
- 6.66 The errors had a large impact on the net PBS/RPBS cost of inclisiran, with corrected estimates totalling > \$1 billion over 6 years compared to \$200 million to < \$300 million over 6 years in the submission based on published prices of inclisiran and PCSK9 inhibitors.
- 6.67 Key inputs used to determine the extent of inclisiran use is presented in Table 14.

Table 14: Key inputs for financial estimates

Parameter	Values and source	Commentary on the submission
Patients who would otherwise be treated with ezetimibe		
Patients on PBS-subsidised ezetimibe	521,232 in Year 1 increasing to 734,446 in Year 6. Based on a 10% PBS sample analysis of patients on ezetimibe with or without a statin in March 2022, extrapolated using a 7.1% fixed yearly growth rate.	DUSC considered the use of a fixed growth rate to be acceptable as the non-linear growth was likely to continue.
Proportion of patients on PBS-subsidised ezetimibe with ASCVD	64%. Based on a 10% PBS sample analysis of ezetimibe with or without a statin and streamlined authority codes in September 2018.	Overall, the estimated proportion of patients on ezetimibe with ASCVD is more representative of a floor estimate, with the actual proportion likely to be greater than estimated in the submission. DUSC commented that there is inherent uncertainty associated with combining multiple data sources and proxy indicators. DUSC agreed that there was substantial uncertainty with the size of the ASCVD population.
Proportion of patients with LDL ≥ 1.8 mmol/L	100%. Assumed. As Australian guidelines recommend target lipid levels of <1.8 mmol/L for secondary prevention, it was assumed that all patients on ezetimibe with ASCVD would have LDL ≥ 1.8 mmol/L.	The proportion of patients initiating ezetimibe treatment with LDL ≥ 1.8 mmol/L is uncertain given the absence of a specific threshold in the restriction and more aggressive LDL targets being proposed in international guidelines.
Proportion of patients with additional high-risk factors	52.8%. Based on the proportion of ASCVD patients with additional high-risk factors derived from an analysis of the FOURIER trial population who met eligibility criteria in the non-familial hypercholesterolaemia restriction for evolocumab (para 6.57 and 6.58, evolocumab PSD, July 2019 PBAC meeting).	This estimate was based on patients enrolled in the FOURIER trial with a baseline LDL ≥ 1.8 mmol/L, which may not be applicable to all patients who qualified for ezetimibe given the absence of an LDL threshold in the restriction.
Uptake rates	20% in Year 1 increasing to 50% in Years 5 and 6. Assumed.	The assumptions informing the uptake rates were unclear but resulted in slowing uptake over time in the initiating population. DUSC commented a six-monthly treatment may be appealing to patients who see their doctor every six months.
Patients who would otherwise be treated with statin alone (market growth)		
Patients on PBS-subsidised high intensity statin alone	941,321 in Year 1 increasing to 1,326,376 in Year 6. Based on a 10% PBS sample analysis of patients on high intensity statins in July 2022. The submission included all patients on maximum dose statin and assumed 50% of patients on a high dose statin were on their maximum tolerated dose. Estimates were extrapolated using the same growth rate as for the ezetimibe market (7.1% yearly).	It was unclear how the 10% PBS sample analysis handled patients on statins who may also be on ezetimibe. Growth rates based on patients treated with ezetimibe may not be applicable to patients treated with statins. The analysis may not be applicable to the proposed restriction as it should be based on patients on the maximum tolerated dose of a high potency statin (i.e. atorvastatin or rosuvastatin at any dose).
Proportion of patients with LDL ≥ 1.8 mmol/L	40%. Retrospective analysis of medical records in the MedicineInsight database covering LDL measures and use of lipid-lowering therapies between 2010 and 2019 in patients with ASCVD (Code Red report, Carrington 2020).	DUSC noted this source presents nine years of records and began 13 years ago. DUSC commented there was high uncertainty associated with this assumption as the retrospective analysis was the sole data source.

Public Summary Document - March 2023 PBAC Meeting with May 2023 Addendum

Parameter	Values and source	Commentary on the submission
Proportion of patients with ASCVD	60.2%. Based on a retrospective analysis of health records from a US Midwestern health system (Sidebottom 2020). The study estimated that of 38,755 patients on high intensity statins, 23,353 of patients also had ASCVD.	The estimate was based on patients on high intensity statins, which may not be applicable to patients on maximum tolerated doses of high potency statins who have LDL ≥ 1.8 mmol/L. The applicability of estimates derived from the US setting to the Australian setting is uncertain. DUSC commented that the assumptions used to identify ASCVD were poorly justified and likely underestimated the population size.
Proportion of patients with additional high-risk factors	52.8%. Assumed the same as for patients on ezetimibe.	The estimate was based on an analysis of the FOURIER trial population.
Uptake rates	7.5% in Year 1 increasing to 15% in Years 3, 4, 5 and 6. Assumed.	The assumptions behind the uptake rates were unclear but resulted in slowing uptake over time. DUSC commented a six-monthly treatment may be appealing to patients who see their doctor every six months.
Inclisiran utilisation		
Treatment persistence	92.3%. Based on the proportion of patients receiving their 3rd inclisiran dose (Day 270) in the ORION-10 trial.	The estimate was inconsistent with treatment persistence rates (96.8% per year) applied in the economic model based on data from the ASCVD subgroup of the ORION-10 and ORION-11 trials. DUSC considered that ezetimibe discontinuation rates would be informative to this assumption.
Treatment compliance	85%. Based on the rate reported in a review of statin therapies in 2012, as recommended by PBAC in November 2019 (para 4.30, evolocumab PSD, November 2019 PBAC meeting).	This was inconsistent with assumed perfect adherence in the economic model of the submission. While the PBAC previously recommended an 85% compliance rate for evolocumab, it is unclear whether this recommendation can be extended to inclisiran due to differences in dosing frequency.
Cost offsets associated with substituted use of ezetimibe on the PBS/RPBS		
Prevalent population on inclisiran	35,227 in Year 1 increasing to 124,092 in Year 6. Based on estimated total number of inclisiran treated patients, in patients otherwise treated with ezetimibe.	These estimates were highly uncertain due to concerns with treated population estimates.
Proportion of patients who discontinue ezetimibe	93%. Based on the complement of average baseline use of ezetimibe in the ORION-10 (10%) and ORION-11 (4%) trials, calculated as 7% in the submission.	The assumption that inclisiran would replace rather than be used in addition to ezetimibe was inadequately justified given the minimal treatment burden associated with ezetimibe and wide availability of ezetimibe with statin fixed dose combinations.
Ezetimibe treatment compliance	85%. Based on the rate reported in a review of statin therapies in 2012, as recommended by PBAC in November 2019 (para 4.30, evolocumab PSD, November 2019 PBAC meeting).	The assumption that ezetimibe has the same pattern of compliance as inclisiran and PCSK9 inhibitor therapies was inadequately justified given differences in both frequency and mode of administration.
Cost offsets due to avoided use of subsequent-line therapies on the PBS/RPBS		
Patients initiating inclisiran	35,227 in Year 1 decreasing to 17,147 in Year 6.	These estimates were highly uncertain due to concerns with treated population estimates.
Proportion of patients alive with LDL ≥ 1.8 mmol/L, that are eligible for PCSK9 inhibitor therapies	56.8%. Based on the cumulative proportion of patients in subsequent-line health states of the economic model at year 2, including deaths.	The proportion of patients with LDL ≥ 1.8 mmol/L in the model was dependent on the modelled baseline LDL levels from the high-risk subgroups of the ORION trial program as well as modelled efficacy of ezetimibe based on the EASE trial. The applicability of these estimates to clinical practice is unclear.

Public Summary Document - March 2023 PBAC Meeting with May 2023 Addendum

Parameter	Values and source	Commentary on the submission
PCSK9 uptake rate	100%. Assumed.	DUSC considered that the assumption that all patients with LDL ≥ 1.8 mmol/L despite ezetimibe would be treated with PCSK9 may not be reasonable.
Proportion of patients who are alive and persist with PCSK9 therapies	94.7% in Year 2 decreasing to 94.1% in Year 6.	Persistence estimates in the economic model were based on data from the ASCVD subgroup of the ORION-10 and ORION-11 trials (96.8%), higher than estimated for inclisiran in the budget impact analysis (92.3%). The use of a higher estimate was inappropriate as it resulted in greater cost offsets associated with substituted PCSK9 inhibitor therapies, than if based on the proportion of patients persisting with inclisiran treatment in the budget impact model.
PCSK9 treatment compliance	85%. Based on the rate reported in a review of statin therapies in 2012, as recommended by PBAC in November 2019 (para 4.30, evolocumab PSD, November 2019 PBAC meeting).	The submission did not adequately justify the use of the unadjusted compliance estimate (capturing both adherence and persistence) given persistence was already applied to treated patient estimates (see above).

Source: Sections 4.1-4.5 and Section 4_Utilisation and financial estimates_inclisiran Excel workbook of the submission

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

- 6.68 The estimated use and financial impact of inclisiran based on the published price of inclisiran and published prices of PCSK9 inhibitors, including corrections for errors in the submission is summarised in the Table 15.
- 6.69 Estimated cost offsets due to avoided PCSK9 use were calculated in the submission using November 2022 published DPMQs for evolocumab and alirocumab. Published prices for evolocumab were updated in December 2022 (evolocumab 140 mg DPMQ \$337.94, evolocumab 420 mg DPMQ \$365.36) reflecting the expansion of the listing based on a lower LDL threshold of 1.8 mmol/L compared to 2.6 mmol/L previously. Financial estimates based on published prices were not updated during the evaluation.

Table 15: Estimated use and financial implications (published prices)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of inclisiran						
Number of patients who would otherwise be on ezetimibe	■ ¹	■ ²	■ ³	■ ⁴	■ ⁵	■ ⁵
Number of patients who would otherwise be on statin alone	■ ⁶	■ ⁷	■ ⁸	■ ⁸	■ ⁸	■ ⁸
Total scripts dispensed	■ ⁵	■ ⁵	■ ⁹	■ ⁹	■ ⁹	■ ⁹
Estimated financial implications of inclisiran						
Cost to PBS/RPBS less co-payments (\$)	■ ¹⁰	■ ¹¹	■ ¹²	■ ¹³	■ ¹⁴	■ ¹⁴
Estimated financial implications due to changes in use of other medicines						
PBS/RPBS cost offset less co-payments for ezetimibe monotherapy and ezetimibe/statin combinations (\$)	■ ¹⁵	■ ¹⁵	■ ¹⁵	■ ¹⁵	■ ¹⁵	■ ¹⁵
PBS/RPBS cost offset less co-payments for avoided use of subsequent-line PCSK9 (\$)	■ ¹⁵	■ ¹⁵	■ ¹⁵	■ ¹⁵	■ ¹⁵	■ ¹⁵
Net financial implications						
Net cost to PBS/RPBS (\$)	■ ¹⁷	■ ¹⁷	■ ¹⁰	■ ¹⁰	■ ¹⁰	■ ¹⁰
MBS cost of inclisiran administration (\$)	■ ¹⁶	■ ¹⁶	■ ¹⁶	■ ¹⁶	■ ¹⁶	■ ¹⁶
MBS cost offset due to avoided PCSK9 administrations (\$)	■ ¹⁵	■ ¹⁵	■ ¹⁵	■ ¹⁵	■ ¹⁵	■ ¹⁵
Net cost to Government (\$)	¹⁷	■ ¹⁷	■ ¹⁰	■ ¹⁰	■ ¹⁰	■ ¹⁰

Source: Section 4 _Utilisation and financial estimates_ inclisiran Excel workbook of the submission

Italicised estimates were calculated during the evaluation, correcting for multiple errors in the submission

The redacted values correspond to the following ranges:

¹ 30,000 to < 40,000

² 50,000 to < 60,000

³ 80,000 to < 90,000

⁴ 90,000 to < 100,000

⁵ 100,000 to < 200,000

⁶ 5,000 to < 10,000

⁷ 10,000 to < 20,000

⁸ 20,000 to < 30,000

⁹ 200,000 to < 300,000

¹⁰ \$300 million to < \$400 million

¹¹ \$400 million to < \$500 million

¹² \$500 million to < \$600 million

¹³ \$600 million to < \$700 million

¹⁴ \$700 million to < \$800 million

¹⁵ net cost saving

¹⁶ \$0 to < \$10 million

¹⁷ \$200 million to < \$300 million

- 6.70 The estimated net cost to Government for inclisiran including PBS/RPBS and MBS cost offsets was \$200 million to < \$300 million in Year 1, increasing to \$300 million to < \$400 million in Year 6, a total of > \$1 billion over 6 years. This was substantially higher than the submission's estimate of \$100 million to < \$200 million over 6 years.
- 6.71 The estimated extent of use of inclisiran should not be considered reliable due to uncertainties with key sources and parameters used to determine the size of the eligible and treated populations, and circumstances of use of inclisiran.
- 6.72 The submission did not account for increased costs associated with the additional use of statin therapies in the majority of patients (approximately 65% of all ezetimibe scripts based on 2021 PBS/RPBS utilisation data) who discontinued ezetimibe/statin fixed dose combinations.

- 6.73 Estimated cost offsets due to avoided PCSK9 use were dependent on highly uncertain treated population estimates for inclisiran as well as uncertainties associated with key inputs derived from the economic model of the submission. The resulting avoided patient-years of treatment with PCSK9 inhibitor therapies may not be plausible given the estimates (e.g. 20,009 in Year 1) were substantially higher than the estimated total number of patients treated with PCSK9 inhibitor therapies in the 2021-2022 financial year (approximately 1,098 patients assuming perfect compliance). Uptake of PCSK9 inhibitor therapies in the future is likely to change given the recent expansion of the evolocumab listing in December 2022 (lowering of LDL threshold from 2.6 mmol/L to 1.8 mmol/L and initiation of evolocumab by any medical practitioner).
- 6.74 MBS costs associated with health professional attendance for administrations of treatment are not appropriate for inclusion in the estimates of utilisation and financial implications.

Quality Use of Medicines

- 6.75 The submission stated that the sponsor is developing several initiatives and partnerships to improve cardiovascular healthcare, as part of the broader inclisiran Australian launch plan. The submission did not address potential non-adherence to oral hypercholesterolaemia treatments associated with the use of inclisiran. Results from subgroup analyses of the ORION trials suggested that patients who were close to target LDL-C levels had large increases in LDL-C levels over time due to non-adherence to background oral treatments. This may reflect an underlying quality use of medicines issue with the availability of treatment options that have less frequent dosing.
- 6.76 DUSC noted that inclisiran represents a new mechanism of action and suggested the sponsor should propose QUM education for prescribers prior to PBS listing and post market pharmacovigilance activities.

Financial Management – Risk Sharing Arrangements

- 6.77 No risk-sharing arrangement (RSA) was proposed for inclisiran. There is an established two-tier subsidisation cap arrangement on forecast utilisation for current PBS listings of PCSK9 inhibitors (para 6.58, evolocumab PSD, July 2022 PBAC meeting). It may be appropriate for inclisiran to be part of established risk-sharing arrangements for PCSK9 inhibitors given the use of inclisiran will affect the utilisation of PCSK9 inhibitors. The pre-PBAC response stated that the Sponsor would be willing to join the current PCSK9 inhibitor RSA if it was recommended in the third line setting.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend inclisiran for the treatment of hypercholesterolaemia and ASCVD. The PBAC considered the proposed positioning of inclisiran as a second-

line alternative to ezetimibe was not justified. The PBAC considered inclisiran would be most appropriately positioned as an alternative to the PCSK9 inhibitors in the third-line setting. The PBAC noted the submission presented supporting indirect treatment comparisons (ITCs) between inclisiran and the PCSK9 inhibitors; however, it considered that, given the results consistently favoured evolocumab over inclisiran and there was no assessment of either a minimum clinically important difference (MCID) or non-inferiority margin, non-inferiority to the PCSK9 inhibitors was uncertain. To address the uncertainty in the non-inferiority claim, an early re-entry resubmission using a CMA with a lower price than evolocumab (in the order of 10%) would be required to support PBS listing in the same treatment setting as evolocumab for non-FH and HeFH. The PBAC considered that revised PBS restrictions and financial estimates would also be required to align with the updated CMA.

- 7.2 The PBAC considered that the proposed place in therapy for inclisiran, as a second line treatment for use in patients with hypercholesterolaemia and ASCVD who are unable to achieve target lipid thresholds with statins alone or who are intolerant to statin therapy, was not justified for the reasons outlined in paragraph 1.4. The PBAC considered that inclisiran would be most appropriately positioned as an alternative to the PCSK9 inhibitors in the subsequent treatment line to statins and/or ezetimibe.
- 7.3 The PBAC considered there was a moderate clinical need for this alternative PCSK9 inhibitor, noting the clinician hearing and consumer comments described the likely improved adherence from twice yearly dosing for some patients, particularly those in rural and remote areas and older patients.
- 7.4 The PBAC considered PCSK9 inhibitor therapies (evolocumab and alirocumab) the appropriate comparator for the third line setting. As noted in paragraph 7.2, the PBAC did not consider there was a role for inclisiran as an alternative to ezetimibe in the second line setting. The PBAC noted that the alirocumab PBS listing had not been extended following the July 2022 recommendation to (i) include patients who have a LDL-C level between 1.8 and 2.6 mmol/L despite optimised treatment with statins and ezetimibe, and (ii) allow initial prescribing by any medical practitioner in consultation with a specialist physician. The PBAC therefore considered inclisiran would most appropriately be considered as an alternative to the evolocumab eligible population in non-FH and HeFH.
- 7.5 The PBAC noted the comparative clinical effectiveness of inclisiran with PCSK9 inhibitors was based on a series of ITCs, which compared the results from the key inclisiran trials (ORION 9, ORION 10, and ORION 11) versus evolocumab and alirocumab trials, using placebo as the common comparator. The PBAC noted that there were transitivity and heterogeneity issues between the various trials which may have limited the exchangeability of the outcomes of the ITCs. The PBAC also noted that sensitivity analyses using different imputation methods introduced a substantial degree of heterogeneity between the inclisiran trials (see Table 4).
- 7.6 The PBAC noted that, although some of the ITCs between inclisiran and evolocumab

(those in patients with ASCVD and from Burnett 2022; see Table 6) did not demonstrate a statistically significant difference in terms of the mean percentage change in LDL-C from baseline, the point estimates favoured evolocumab. For other comparisons (those in patients with HeFH and from Huang 2022 and Toth 2022; see Table 6) the ITCs indicated that evolocumab was statistically significantly superior to inclisiran in terms of the mean percentage change in LDL-C from baseline.

- 7.7 The PBAC noted that the comparisons versus alirocumab demonstrated no statistically significant differences in terms of the mean percentage change in LDL-C from baseline in patients with ASCVD and HeFH and in Burnett 2022 and Huang 2022 which considered the low (75 mg fortnightly or 300 mg monthly) and high (150 mg fortnightly) doses of alirocumab together (i.e. in patients who did not respond to the low dose and moved to the high dose of alirocumab). The PBAC noted that the results from Toth 2022 indicated that although the comparisons with low dose alirocumab did not demonstrate a statistically significant difference, the comparison with high dose alirocumab was statistically significantly in favour of alirocumab.
- 7.8 The PBAC noted that there was no assessment of either a MCID or non-inferiority margin in the submission, which meant inferiority to high dose alirocumab and evolocumab could not be ruled out.
- 7.9 The PBAC also noted that the comparative efficacy and safety of inclisiran in statin-intolerant patients remained unknown and considered this was a significant limitation given the extensive body of evidence supporting the use of PCSK9 inhibitors in this population.
- 7.10 The PBAC noted that the submission claimed that inclisiran was non-inferior compared to the PCSK9 inhibitors. Overall, the PBAC considered that inclisiran was likely non-inferior to low dose alirocumab, but that the non-inferiority claim compared to evolocumab was uncertain for the non-FH with ASCVD population. The PBAC also considered that inclisiran was inferior to evolocumab for the HeFH population given statistically significantly worse results for inclisiran compared to evolocumab.
- 7.11 In terms of safety, the PBAC noted that the submission did not present any comparative data versus the nominated comparators. The PBAC noted that inclisiran was reasonably well-tolerated compared to placebo. The PBAC considered that although inclisiran was likely comparable to the PCSK9 inhibitors, the claim of non-inferior safety was uncertain.
- 7.12 The PBAC noted that the submission presented a cost utility analysis (CUA) versus ezetimibe and a supportive CMA versus PCSK9 inhibitors. The PBAC noted that the CUA included a treatment switching rule for ezetimibe patients that resulted in two distinct modelled patient populations based on whether patients were eligible or ineligible for PCSK9 inhibitor therapy. The PBAC agreed with the ESC that this resulted in a misleading base case incremental cost effectiveness ratio (ICER; see paragraph 6.46) and, along with several other inputs and assumptions identified in the sensitivity

analyses (see Table 11), made the CUA unreliable. As the PBAC considered that inclisiran should have been positioned as a third line treatment, the CUA was not informative for decision making.

- 7.13 The PBAC was unable to accept the CMA versus PCSK9 inhibitors as presented in the submission due to the uncertainty with the claim of non-inferior efficacy (see paragraph 7.10). The PBAC noted that the CMA used evolocumab as a proxy for the PCSK9 inhibitors which was considered appropriate to qualify for the same PBS listings as evolocumab for non-FH with ASCVD and HeFH. The PBAC advised that an early re-entry resubmission with a revised CMA offering a lower price than evolocumab (in the order of 10%) to address the uncertainty in the clinical claim would be required.
- 7.14 Alternatively, a standard re-entry resubmission would need to include further justification of non-inferiority and equivalent pricing compared to evolocumab for the non-FH with ASCVD population, with assessment of the MCID and a non-inferiority margin, further consideration of selected trials for inclusion in the comparative analysis, and address the issues raised in the evaluation regarding use in the statin intolerant population. A lower price than evolocumab for HeFH would be required given inclisiran was inferior to evolocumab in this indication.
- 7.15 The PBAC considered that a future resubmission would need revised utilisation and financial impact estimates which aligned with the updated CMA. For an early re-entry resubmission, these estimates should be based on a market share approach, with consideration of the cost of improved adherence as suggested in paragraph 7.3.
- 7.16 The PBAC noted the offer in the pre-PBAC response that the Sponsor would be willing to join the current PCSK9 inhibitor risk-sharing arrangement if it was recommended in the third line setting. The PBAC considered that this would be an appropriate approach for a future resubmission given the listing of inclisiran would not be intended to provide an additional line of therapy and the Government should not bear the risk of any additional cost.
- 7.17 The PBAC considered that any future resubmission should propose restrictions for inclisiran that were based on the current PBS restrictions for evolocumab for use in HeFH and non-FH with symptomatic ASCVD.
- 7.18 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for inclisiran using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation:
- Provide a revised CMA between inclisiran and evolocumab with a price offer as outlined in paragraph 7.13;
 - Provide revised financial impact estimates that align with the updated CMA as outlined in paragraph 7.15;

- Provide revised restrictions that align with the current PBS restrictions for evolocumab as outlined in paragraph 7.17.
- 7.19 The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.
- 7.20 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The sponsor had no comment.

Addendum to the March 2023 PBAC PSD:

7.02 INCLISIRAN,

Injection 284 mg in 1.5 mL single use pre-filled syringe,

Leqvio[®],

Novartis Pharmaceuticals Australia Pty Limited.

10 Background

10.1 At the March 2023 PBAC meeting, the PBAC did not recommend inclisiran for the treatment of hypercholesterolaemia and ASCVD. However, the PBAC did consider that the outstanding issues could be easily resolved in a simple resubmission for inclisiran using the early re-entry pathway. As per paragraph 7.18, the PBAC identified that a resubmission should present:

- a CMA comparing inclisiran with evolocumab, which resulted in a price in the order of 10% lower than evolocumab to address the uncertainty in the clinical claim of non-inferior efficacy;
- revised financial estimates that aligned with the revised CMA; and
- revised restrictions that aligned with the current PBS restrictions for evolocumab in patients with HeFH and non-FH with symptomatic ASCVD.

10.2 The PBAC also previously considered it appropriate that inclisiran join the risk sharing arrangement for the currently listed PCSK9 inhibitors (evolocumab and alirocumab) if it was recommended in the third line setting. The listing of inclisiran would not be intended to provide an additional line of therapy and the Government should not bear the risk of any additional cost (paragraph 7.16).

11 Requested listing

11.1 The resubmission provided revised initial, continuing and grandfather restrictions for inclisiran that aligned with those for evolocumab for HeFH and non-FH with symptomatic ASCVD patients.

11.2 The resubmission proposed criteria that would allow patients to switch between inclisiran and the PCSK9 inhibitors.

11.3 The resubmission stated that there would be between 500 to < 5,000 patients enrolled in a patient familiarisation program that would require transitioning to PBS-subsidised treatment with a grandfathering restriction.

12 Consideration of the evidence

Clinical claim

12.1 In March 2023, the PBAC considered that (paragraphs 7.10 and 7.11):

- inclisiran was likely non-inferior in terms of efficacy compared to low dose alirocumab,
- the claim that inclisiran was non-inferior compared to evolocumab in terms of efficacy was uncertain for the non-FH with ASCVD population;
- inclisiran was inferior in terms of efficacy compared to evolocumab in the HeFH population; and
- the claim that inclisiran was non-inferior in terms of safety compared to the PSCK9 inhibitors was uncertain.

12.2 No new data was presented in the resubmission.

Economic analysis

12.3 In March 2023, the PBAC was unable to accept the CMA versus evolocumab, as a proxy for all PSCK9 inhibitors, due to the uncertainties with the claims of non-inferior efficacy and advised that, to address the uncertainties, the price of inclisiran should be in the order of 10% lower than evolocumab (see paragraph 7.13).

12.4 The resubmission presented an updated CMA which was based on the published evolocumab prices from the December 2022 PBS schedule. It was otherwise unchanged. To address uncertainties identified during the March 2023 consideration, the resubmission proposed that a price discount of 10% be applied to the cost minimised effective price of inclisiran.

Table 16: Updated results of the CMA

Evolocumab	140 mg once fortnightly	420 mg once monthly
Cost per dose (published AEMP)	\$146.50	\$317.30
Dose duration	2 weeks	1 month
Total doses (over 27 months)	58.7	27.0
Total medicine cost 27 months	\$8,599.55	\$8,567.10
Total administration cost	\$0	\$0
Total drug + administration costs	\$8,599.55	\$8,567.10
PBS usage (evolocumab)	84.60%	15.40%
Weighted average cost of evolocumab	\$8,594.55	
Inclisiran	284 mg (at 0 months, 3 months and then every 6 months)	
Total doses (over 27 months)	5	
Total drug + administration costs (\$)		
Total administration costs (= 5 x \$18.20; MBS item 3)	\$91.00	
Total drug costs (\$ - \$91.00) (\$)		
Published AEMP (total drug costs divided by number of doses) (\$)		
Evolocumab SPA rebate	Unknown	
Published AEMP minus rebate (Published AEMP x (1-rebate)) (\$)		
Proposed inclisiran discount		%
Effective AEMP (Published AEMP minus SPA x (1-%)) (\$)		

Source: Table 1 of the early re-entry submission

AEMP = approved ex-manufacturer price; MBS = Medicare Benefits Schedule; SPA = special pricing arrangement

- 12.5 Based on the CMA and including the % discount, the resubmission estimated that the published ex-manufacturer price of inclisiran would be \$| (DPMQ = \$|).

Estimated PBS usage and financial implications

- 12.6 In March 2023, the PBAC advised that revised utilisation and financial impact estimates which (i) aligned with the updated CMA; (ii) were based on a market share approach; and (iii) considered the cost of improved adherence, would be required (paragraph 7.15).
- 12.7 The resubmission presented revised estimates based on a market share approach that assumed that inclisiran would substitute for evolocumab and alirocumab. The key inputs are summarised in the table below.

Table 17: Key inputs for financial estimates

Parameter	Values and source
Market for evolocumab and alirocumab	- PBS items numbers for evolocumab (11484K, 11985T, 11986W, 11485L) and alirocumab (12607M, 12608N, 12604J, 13613W) in non-FH and HeFH patients. - non-FH and HeFH PBS scripts dispensed between 2019 and 2022 were assumed to represent script numbers in patients with LDL $\geq$ 2.6 mmol/L. Total scripts are expected to increase at a slower rate over the first 6 years of listing. - script numbers for patients with LDL $\geq$ 1.8 < 2.6 mmol/L were assumed to be equal to the midpoint of the range provided in the July 2022 evolocumab PSD.
Substitution of evolocumab and alirocumab with inclisiran	Year 1: 15%, Year 2: 20% Year 3: 33%; Year 4: 33%; Year 5: 33%; Year 6: 33% Substitution was considered to be equal across evolocumab and alirocumab (i.e. in Year 1 inclisiran substituted for 15% of evolocumab scripts and 15% of alirocumab scripts).
Grandfather patients	Assumed to be captured within the script estimates for the recently expanded evolocumab listing.
Adherence	Evolocumab = 80% remain on treatment over 12 months (evolocumab DUSC analysis, February 2023) Alirocumab = 80% (assumed to be equal to evolocumab) Inclisiran = 88% (assumption, due to 6-monthly dosing)

Source: early re-entry submission

HeFH = heterozygous familial hypercholesterolaemia; LDL = low-density lipoprotein; non-FH = non-familial hypercholesterolaemia; PBS = Pharmaceutical Benefits Scheme

12.8 The results of the revised financial impact estimates are presented in Table 18.

Table 18: Revised financial impact estimates

	Year 1 (2023)	Year 2 (2024)	Year 3 (2025)	Year 4 (2026)	Year 5 (2027)	Year 6 (2028)
Total and substituted market non-FH and HeFH market						
Evolocumab script numbers	¹	¹	²	²	²	²
Alirocumab script numbers	³	³	⁴	⁴	⁴	⁴
Inclisiran uptake	15%	20%	33%	33%	33%	33%
Evolocumab substituted scripts	⁵	⁵	⁷	⁷	⁷	⁷
Alirocumab substituted scripts	⁸	⁸	⁸	⁸	⁸	⁸
Script numbers and financial impact assuming equal adherence						
Inclisiran script numbers	⁸	⁸	⁴	⁴	⁴	⁴
Total cost to PBS/RBS of inclisiran (after co-payment) (\$)	⁹	¹⁰	¹¹	¹¹	¹¹	¹¹
Cost savings to PBS/RBS from substituted evolocumab and alirocumab scripts (after co-payment) (\$)	⁹	¹⁰	¹¹	¹¹	¹²	¹²
Net cost to PBS/RBS (after co-payment) (\$)	¹³	¹³	¹³	¹³	¹³	¹³
PBAC recommended changes						
Inclisiran uptake	20%	30%	40%	50%	50%	50%
Total cost of PBS/RPBS of inclisiran (after co-payment) (\$)	¹⁰	¹¹	¹²	¹²	¹⁴	¹⁴
Cost savings to PBS/RBS from substituted evolocumab and alirocumab scripts (after co-payment) (\$)	¹⁰	¹¹	¹⁴	¹⁴	¹⁴	¹⁴
Net cost to PBS/RPBS (after co-payment) (\$)	¹³	¹³	¹³	¹³	¹³	¹³

Source: Table 4 of the early re-entry submission

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

The redacted values correspond to the following ranges:

¹100,000 to < 200,000²200,000 to < 300,000³5,000 to < 10,000⁴10,000 to < 20,000⁵20,000 to < 30,000⁶50,000 to < 60,000⁷80,000 to < 90,000⁸500 to < 5,000⁹\$0 to < \$10 million¹⁰\$10 million to < \$20 million¹¹\$20 million to < \$30 million¹²\$30 million to < \$40 million¹³net cost saving¹⁴\$40 million to < \$50 million

12.9 The resubmission estimated that the listing of inclisiran on the PBS/RPBS would result in a cost saving of approximately \$0 to < \$10 million in Year 1, increasing to \$0 to < \$10 million in Year 6 based on published prices. The resubmission stated that the cost saving was driven by the proposed 1% price reduction for inclisiran and a reduction in dispensing fees.

- 12.10 The resubmission estimated an increased cost to the MBS associated with the need for health care professional administration of inclisiran. However, the Secretariat noted this cost should not be included in the financial impact estimates.

13 PBAC Outcome

- 13.1 The PBAC recommended inclisiran for the treatment of HeFH and non-FH with ASCVD. The PBAC considered that the positioning of inclisiran as a third-line treatment as an alternative to the PCSK9 inhibitors (evolocumab and alirocumab) was appropriate. The PBAC considered the clinical effectiveness of inclisiran was comparable to evolocumab, although non-inferiority could not be confirmed due to the issues identified in March 2023 (see paragraphs 7.6 and 7.8). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of inclisiran would be acceptable if the cost minimised price to evolocumab was reduced by the discount offered in the resubmission. The PBAC noted that the resubmission had addressed the outstanding issues from the March 2023 submission and considered that the lower price offered in the CMA and revised financial estimates were reasonable.
- 13.2 The PBAC recalled that in March 2023 it had considered that inclisiran would be most appropriately positioned as an alternative to the PCSK9 inhibitors as a third line treatment and that a resubmission should provide a revised CMA between inclisiran and evolocumab that resulted in a price of inclisiran that was in the order of 10% lower than the current price of evolocumab; revised financial estimates that aligned with the updated CMA; and revised restrictions that aligned with the current PBS restrictions for evolocumab (see paragraph 7.18).
- 13.3 The PBAC recalled that it had previously considered that the claim that inclisiran was non-inferior to the PCSK9 inhibitors in terms of efficacy in the treatment of non-FH with ASCVD was uncertain and that inclisiran was inferior to evolocumab in the treatment of HeFH (see paragraph 7.10). Further, the PBAC recalled that a price reduction compared to evolocumab would be required to address the uncertainties in the claims of non-inferiority.
- 13.4 The PBAC noted that the resubmission presented an updated CMA between inclisiran and evolocumab that was based on the December 2022 prices for evolocumab. The PBAC noted that otherwise, the CMA was unchanged. The PBAC considered that this was reasonable. The PBAC also noted that the resubmission proposed that a price discount of 1% would be applied to the cost minimised effective approved ex-manufacturer price (AEMP) of inclisiran to address the uncertainties associated with the clinical claim. The PBAC considered that the proposed price discount was acceptable.
- 13.5 The PBAC noted that the resubmission provided revised financial impact estimates that (i) aligned with the updated CMA; (ii) were based on a market share approach; and (iii) considered the cost of improved adherence as outlined in paragraph 7.15.

- 13.6 The PBAC noted that the resubmission assumed that the substitution of evolocumab and alirocumab for inclisiran would be 15% in Year 1, 20% in Year 2 and 33% in Years 3 to 6. The PBAC considered that the assumed uptake rates were conservative, particularly as there was a large eligible population that was not currently being treated with the PCSK9 inhibitors, inclisiran had a manageable safety profile and inclisiran required 6-monthly maintenance injections, as compared to two or four weekly injections for the PCSK9 inhibitors. There is also GP prescribing available for continuing treatment. The PBAC considered that uptake would likely be in the range of 20% in Year 1, 30% in Year 2, 40% in Year 3 and 50% in Years 4 to 6.
- 13.7 The PBAC noted that the resubmission assumed that there would be a 10% improvement in adherence due to the 6-monthly dosing schedule of inclisiran. The PBAC considered that this was a reasonable assumption.
- 13.8 Overall, the PBAC considered that, due to the [REDACTED] % price reduction for inclisiran and a reduction in dispensing fees, the listing of inclisiran on the PBS/RPBS would be cost saving.
- 13.9 The PBAC noted that the resubmission assumed that there would be a cost to the MBS due to inclisiran requiring administration by a health care professional every 6 months. The PBAC considered that it was unlikely that this cost would be recognised as patients with high risk HeFH or non-FH would visit their clinician twice a year. Regardless, it was noted that MBS costs/savings due to professional attendance are not realised by the health system and they cannot be included in the financial impact estimates.
- 13.10 The PBAC considered that inclisiran should join the current PCSK9 inhibitor risk sharing arrangement, given the listing of inclisiran would not provide an additional line of therapy.
- 13.11 The PBAC noted that the resubmission provided revised initial, continuing and grandfather restrictions for inclisiran that aligned with those for evolocumab for HeFH and non-FH with ASCVD. The PBAC considered that this was appropriate, noting the grandfathered patients would need to have met the initial restriction criteria when they commenced inclisiran to be eligible for grandfathering. The PBAC also noted that the resubmission proposed criteria that would allow patients to switch between inclisiran and the PCSK9 inhibitors. The PBAC noted that flow on restriction changes would be required to allow for switching between inclisiran and evolocumab and alirocumab. The PBAC also noted that flow on restrictions changes would be required to prevent the concomitant use of inclisiran and the PCSK9 inhibitors.
- 13.12 The PBAC recommended that, under Section 101 (3BA) of the *National Health Act 1953*, inclisiran should not be treated as interchangeable with any other drugs.
- 13.13 The PBAC advised that, like evolocumab and alirocumab, inclisiran is not suitable for prescribing by nurse practitioners.
- 13.14 The PBAC recommended that the Early Supply Rule should not apply to inclisiran.

13.15 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because inclisiran is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over the PCSK9 inhibitors (evolocumab and alirocumab), or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

13.16 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive PBAC recommendation.

Outcome:

Recommended

14 Recommended listing

14.1 Add indications as follows:

Restrictions for HeFH:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty (packs)	Max. qty (units)	No. of Rpts	Available brands
INCLISIRAN					
inclisiran 284 mg/1.5mL injection, 1.5 mL prefilled syringe	New	1	1	1	Leqvio®
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: ☒ Medical Practitioners					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Administrative Advice: Application for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
Episodicity: Chronic					
Severity: Nil					
Condition: Familial heterozygous hypercholesterolaemia					
PBS indication: Familial heterozygous hypercholesterolaemia					
Treatment phase: Initial treatment					
☒ Authority Required – telephone/online					
Clinical criteria					
The treatment must be in conjunction with dietary therapy and exercise,					
AND					
Clinical criteria					
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					
AND					
Clinical criteria					

Public Summary Document - March 2023 PBAC Meeting with May 2023 Addendum

Patient must have an LDL cholesterol level in excess of 1.8 mmol/l in the presence of symptomatic atherosclerotic cardiovascular disease; OR
Patient must have an LDL cholesterol level in excess of 5 mmol/l per litre.
AND
Clinical criteria
Patient must have been treated with the maximum recommended dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily) according to the TGA-approved Product Information or the maximum tolerated dose of atorvastatin or rosuvastatin for at least 12 consecutive weeks 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
AND
Clinical criteria
Patient must have been treated with ezetimibe for at least 12 consecutive weeks in conjunction with a statin (if tolerated), dietary therapy and exercise
AND
Clinical criteria
Patient must not be receiving concomitant PBS-subsidised treatment with a monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9) for this PBS indication.
AND
Treatment criteria:
Must be treated by a specialist physician; OR
Must be treated by a physician who has consulted a specialist physician.
Prescriber instructions:
<i>Monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9) medications are evolocumab or alirocumab</i>
Prescriber instructions:
Symptomatic atherosclerotic cardiovascular disease is defined as: (i) the presence of symptomatic coronary artery disease (prior myocardial infarction, prior revascularisation procedure, angina associated with demonstrated significant coronary artery disease (50% or greater stenosis in 1 or more coronary arteries on imaging), or positive functional testing (e.g. myocardial perfusion scanning or stress echocardiography); or (ii) the presence of symptomatic cerebrovascular disease (prior ischaemic stroke, prior revascularisation procedure, or transient ischaemic attack associated with 50% or greater stenosis in 1 or more cerebral arteries on imaging); or (iii) the presence of symptomatic peripheral arterial disease (prior acute ischaemic event due to atherosclerosis, prior revascularisation procedure, or symptoms of ischaemia with evidence of significant peripheral artery disease (50% or greater stenosis in 1 or more peripheral arteries on imaging)).
The qualifying LDL cholesterol level following at least 12 consecutive weeks of combined treatment with a statin, ezetimibe, dietary therapy and exercise (unless treatment with a statin is contraindicated, or following completion of statin trials as described in these prescriber instructions in the event of clinically important adverse events) must be stated at the time of application, documented in the patient's medical records and must be no more than 8 weeks old.
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.

Public Summary Document - March 2023 PBAC Meeting with May 2023 Addendum

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) unless there is a contraindication (e.g. prior rhabdomyolysis) to the alternative statin. This retreatment should occur after a washout period of at least 4 weeks, or if the creatine kinase (CK) level is elevated, retreatment should not occur until CK has returned to normal.

In the event of a trial of the 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 recommended or maximum tolerated dose has been reached or target LDL-c has been achieved.

The following must be stated at the time of application and documented in the patient's medical records:

- (i) the qualifying Dutch Lipid Clinic Network Score; or
- (ii) the result of genetic testing confirming a diagnosis of familial heterozygous hypercholesterolaemia

One of the following must be stated at the time of application and documented in the patient's medical records regarding prior statin treatment:

- (i) the patient was treated with atorvastatin 80 mg or rosuvastatin 40 mg or the maximum tolerated dose of either for 12 consecutive weeks; or
- (ii) the doses, duration of treatment and details of adverse events experienced with trials with each of atorvastatin and rosuvastatin; or
- (iii) the patient is contraindicated to treatment with a statin as defined in the TGA-approved Product Information.

Name, Restriction, Manner of administration and form	PBS item code	Max. qty (packs)	Max. qty (units)	No. of Rpts	Available brands
INCLISIRAN					
inclisiran 284 mg/1.5mL injection, 1.5 mL prefilled syringe	New	1	1	1	Leqvio®
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: ☒ Medical Practitioners					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Episodicity: Chronic					
Severity: Nil					
Condition: Familial heterozygous hypercholesterolaemia					
PBS indication: Familial heterozygous hypercholesterolaemia					
Treatment phase: Continuing treatment with this drug or switching treatment from a monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9) for this PBS indication					
Restriction type: ☒ Authority Required – STREAMLINED					
Clinical criteria					
Patient must have previously received PBS-subsidised treatment with this drug for this condition, OR					
Patient must have previously received PBS-subsidised treatment with a monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9) for this PBS indication					
AND					
Clinical criteria					
The treatment must be in conjunction with dietary therapy and exercise					
AND					
Clinical criteria					
Patient must not be receiving concomitant PBS-subsidised treatment with a monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9), for this PBS indication.					

Public Summary Document - March 2023 PBAC Meeting with May 2023 Addendum

Prescriber instructions:
 Monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9) medications are evolocumab or alirocumab

Name, Restriction, Manner of administration and form	PBS item code	Max. qty (packs)	Max. qty (units)	No. of Rpts	Available brands
INCLISIRAN					
inclisiran 284 mg/1.5mL injection, 1.5 mL prefilled syringe	New	1	1	1	Leqvio®
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: ☒ Medical Practitioners					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Administrative Advice: Application for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
Episodicity: Chronic					
Severity: Nil					
Condition: Familial heterozygous hypercholesterolaemia					
PBS indication: Familial heterozygous hypercholesterolaemia					
Treatment phase: Grandfather treatment					
☒ Authority Required – telephone/online					
Clinical criteria					
Patient must have received treatment with this drug for this condition prior to [PBS listing date]					
AND					
Clinical criteria					
The treatment must be in conjunction with dietary therapy and exercise,					
AND					
Clinical criteria					
The condition must have been confirmed by genetic testing prior to starting non-PBS-subsidised treatment with this drug for this condition; OR					
The condition must have been confirmed by a Dutch Lipid Clinic Network Score of at least 6 prior to starting non-PBS-subsidised treatment with this drug for this condition					
AND					
Clinical criteria					
Patient must have <i>had</i> an LDL cholesterol level in excess of 1.8 mmol/l in the presence of symptomatic atherosclerotic cardiovascular disease at the time non-PBS-subsidised treatment with this drug for this condition was initiated; OR					
Patient must have <i>had</i> an LDL cholesterol level in excess of 5 mmol/l per litre at the time non-PBS-subsidised treatment with this drug for this condition was initiated.					
AND					
Clinical criteria					
Patient must have been treated with the maximum recommended dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily) according to the TGA-approved Product Information or the maximum tolerated dose of atorvastatin or rosuvastatin for at least 12 consecutive weeks in conjunction with dietary therapy and exercise prior to initiating non-PBS-subsidised treatment with this drug for this condition; OR					
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					

Public Summary Document - March 2023 PBAC Meeting with May 2023 Addendum

Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information
AND
Clinical criteria
Patient must have been treated with ezetimibe for at least 12 consecutive weeks in conjunction with a statin (if tolerated), dietary therapy and exercise prior to initiating non-PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria
Patient must not be receiving concomitant PBS-subsidised treatment with a monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9) for this PBS indication.
AND
Treatment criteria:
Must be treated by a specialist physician; OR
Must be treated by a physician who has consulted a specialist physician.
Prescriber instructions:
<i>Monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9) medications are evolocumab or alirocumab</i>
Prescriber instructions:
Symptomatic atherosclerotic cardiovascular disease is defined as: (i) the presence of symptomatic coronary artery disease (prior myocardial infarction, prior revascularisation procedure, angina associated with demonstrated significant coronary artery disease (50% or greater stenosis in 1 or more coronary arteries on imaging), or positive functional testing (e.g. myocardial perfusion scanning or stress echocardiography); or (ii) the presence of symptomatic cerebrovascular disease (prior ischaemic stroke, prior revascularisation procedure, or transient ischaemic attack associated with 50% or greater stenosis in 1 or more cerebral arteries on imaging); or (iii) the presence of symptomatic peripheral arterial disease (prior acute ischaemic event due to atherosclerosis, prior revascularisation procedure, or symptoms of ischaemia with evidence of significant peripheral artery disease (50% or greater stenosis in 1 or more peripheral arteries on imaging)). The qualifying LDL cholesterol level following at least 12 consecutive weeks of combined treatment with a statin, ezetimibe, dietary therapy and exercise (unless treatment with a statin is contraindicated, or following completion of statin trials as described in these prescriber instructions in the event of clinically important adverse events) must be stated at the time of application, documented in the patient's medical records and must have been no more than 8 weeks old at the time non-PBS-subsidised treatment with this drug for this condition was initiated. A clinically important product-related adverse event is defined as follows: (i) Severe myalgia (muscle symptoms without creatine kinase elevation) which is proven to be temporally associated with statin treatment; or (ii) Myositis (clinically important creatine kinase elevation, with or without muscle symptoms) demonstrated by results twice the upper limit of normal on a single reading or a rising pattern on consecutive measurements and which is unexplained by other causes; or (iii) Unexplained, persistent elevations of serum transaminases (greater than 3 times the upper limit of normal) during treatment with a statin. 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) unless there is a contraindication (e.g. prior rhabdomyolysis) to the alternative statin. This retreat should occur after a washout period of at least 4 weeks, or if the creatine kinase (CK) level is elevated, retreat should not occur until CK has returned to normal. In the event of a trial of the 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 recommended or maximum tolerated dose has been reached or target LDL-c has been achieved. The following must be stated at the time of application and documented in the patient's medical records:

Public Summary Document - March 2023 PBAC Meeting with May 2023 Addendum

(i) the qualifying Dutch Lipid Clinic Network Score; or (ii) the result of genetic testing confirming a diagnosis of familial heterozygous hypercholesterolaemia
One of the following must be stated at the time of application and documented in the patient's medical records regarding prior statin treatment: (i) the patient was treated with atorvastatin 80 mg or rosuvastatin 40 mg or the maximum tolerated dose of either for 12 consecutive weeks; or (ii) the doses, duration of treatment and details of adverse events experienced with trials with each of atorvastatin and rosuvastatin; or (iii) the patient is contraindicated to treatment with a statin as defined in the TGA-approved Product Information.
Prescribing instruction: A patient may qualify for PBS-subsidised treatment under this restriction once only
Prescribing instruction: For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria

Restrictions for non-familial hypercholesterolaemia (non-FH) in patients with symptomatic ASCVD:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty (packs)	Max. qty (units)	No. of Rpts	Available brands
INCLISIRAN					
inclisiran 284 mg/1.5mL injection, 1.5 mL prefilled syringe	New	1	1	1	Leqvio®
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: ☒ Medical Practitioners					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Administrative Advice: Application for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
Episodicity: Chronic					
Severity: Nil					
Condition: Non-familial hypercholesterolaemia					
PBS indication: Non-familial hypercholesterolaemia					
Treatment phase: Initial					
☒ Authority Required – telephone/online					
Clinical criteria					
The treatment must be in conjunction with dietary therapy and exercise,					
AND					
Clinical criteria					
Patient must have symptomatic atherosclerotic cardiovascular disease					
AND					
Clinical criteria					
Patient must have an LDL cholesterol level in excess of 1.8 mmol per litre					
AND					
Clinical criteria					
Patient must have atherosclerotic disease in two or more vascular territories (coronary, cerebrovascular or peripheral vascular					

Public Summary Document - March 2023 PBAC Meeting with May 2023 Addendum

territories); OR
Patient must have severe multi-vessel coronary heart disease defined as at least 50% stenosis in at least two large vessels; OR
Patient must have had at least two major cardiovascular events (i.e. myocardial infarction, unstable angina, stroke or unplanned revascularisation) in the previous 5 years; OR
Patient must have diabetes mellitus with microalbuminuria; OR
Patient must have diabetes mellitus and be aged 60 years or more; OR
Patient must be an Aboriginal or Torres Strait Islander with diabetes mellitus; OR
Patient must have a Thrombolysis in Myocardial Infarction (TIMI) risk score for secondary prevention of 4 or higher.
AND
Clinical criteria
Patient must have been treated with the maximum recommended dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily) according to the TGA-approved Product Information or the maximum tolerated dose of atorvastatin or rosuvastatin for at least 12 consecutive weeks 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
AND
Clinical criteria
Patient must have been treated with ezetimibe for at least 12 consecutive weeks in conjunction with a statin (if tolerated), dietary therapy and exercise
AND
Clinical criteria
<i>Patient must not be receiving concomitant PBS-subsidised treatment with a monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9) for this PBS indication.</i>
AND
Treatment criteria:
Must be treated by a specialist physician; OR
Must be treated by a physician who has consulted a specialist physician.
Prescriber instructions:
<i>Monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9) medications are evolocumab or alirocumab</i>
Prescriber instructions:
Symptomatic atherosclerotic cardiovascular disease is defined as: (i) the presence of symptomatic coronary artery disease (prior myocardial infarction, prior revascularisation procedure, angina associated with demonstrated significant coronary artery disease (50% or greater stenosis in 1 or more coronary arteries on imaging), or positive functional testing (e.g. myocardial perfusion scanning or stress echocardiography); or (ii) the presence of symptomatic cerebrovascular disease (prior ischaemic stroke, prior revascularisation procedure, or transient ischaemic attack associated with 50% or greater stenosis in 1 or more cerebral arteries on imaging); or (iii) the presence of symptomatic peripheral arterial disease (prior acute ischaemic event due to atherosclerosis, prior revascularisation procedure, or symptoms of ischaemia with evidence of significant peripheral artery disease (50% or greater stenosis in 1 or more peripheral arteries on imaging)).
The qualifying LDL cholesterol level following at least 12 consecutive weeks of combined treatment with a statin, ezetimibe, dietary therapy and exercise (unless treatment with a statin is contraindicated, or following completion of statin trials as described in these prescriber instructions in the event of clinically important adverse events) must be stated at the time of application, documented in the patient's medical records and must be no more than 8 weeks old.
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

Public Summary Document - March 2023 PBAC Meeting with May 2023 Addendum

(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.

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) unless there is a contraindication (e.g. prior rhabdomyolysis) to the alternative statin. This retreat should occur after a washout period of at least 4 weeks, or if the creatine kinase (CK) level is elevated, retreat should not occur until CK has returned to normal.

In the event of a trial of the 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 recommended or maximum tolerated dose has been reached or target LDL-c has been achieved.

One of the following must be stated at the time of application and documented in the patient's medical records regarding prior statin treatment:

- (i) the patient was treated with atorvastatin 80 mg or rosuvastatin 40 mg or the maximum tolerated dose of either for 12 consecutive weeks; or*
- (ii) the doses, duration of treatment and details of adverse events experienced with trials of each atorvastatin and rosuvastatin; or*
- (iii) the patient is contraindicated to treatment with a statin as defined in the TGA-approved Product Information.*

One or more of the following must be stated at the time of application and documented in the patient's medical records regarding the presence of cardiovascular disease or high risk of experiencing a cardiovascular event:

- (i) atherosclerotic disease in two or more vascular territories (coronary, cerebrovascular or peripheral vascular territories); or*
- (ii) severe multi-vessel coronary heart disease defined as at least 50% stenosis in at least two large vessels; or*
- (iii) history of at least two major cardiovascular events (i.e. myocardial infarction, unstable angina, stroke or unplanned revascularisation) in the previous 5 years; or*
- (iv) diabetes mellitus with microalbuminuria; or*
- (v) diabetes mellitus and age 60 years or more;*
- (vi) Aboriginal or Torres Strait Islander with diabetes mellitus; or*
- (vii) a Thrombolysis in Myocardial Infarction (TIMI) risk score for secondary prevention of 4 or higher*

Name, Restriction, Manner of administration and form	PBS item code	Max. qty (packs)	Max. qty (units)	No. of Rpts	Available brands
INCLISIRAN					
inclisiran 284 mg/1.5mL injection, 1.5 mL prefilled syringe	New	1	1	1	Leqvio®
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: ☒ Medical Practitioners					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Episodicity: Chronic					
Severity: Nil					
Condition: Non-familial hypercholesterolaemia					
PBS indication: Non-familial hypercholesterolaemia					
Treatment phase: Continuing treatment with this drug or switching treatment from a monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9) for this PBS indication					

Public Summary Document - March 2023 PBAC Meeting with May 2023 Addendum

Restriction type: ☒ Authority Required – STREAMLINED
Clinical criteria
Patient must have previously received PBS-subsidised treatment with this drug for this condition, OR
Patient must have previously received PBS-subsidised treatment with a monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9) for this PBS indication
AND
Clinical criteria
The treatment must be in conjunction with dietary therapy and exercise
AND
Clinical criteria
Patient must not be receiving concomitant PBS-subsidised treatment with a monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9), for this PBS indication.
Prescriber instructions:
Monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9) medications are evolocumab or alirocumab

Name, Restriction, Manner of administration and form	PBS item code	Max. qty (packs)	Max. qty (units)	No. of Rpts	Available brands
INCLISIRAN					
inclisiran 284 mg/1.5mL injection, 1.5 mL prefilled syringe	New	1	1	1	Leqvio®
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: ☒ Medical Practitioners					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Administrative Advice: Application for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
Episodicity: Chronic					
Severity: Nil					
Condition: Non-familial hypercholesterolaemia					
PBS indication: Non-familial hypercholesterolaemia					
Treatment phase: Grandfather treatment					
☒ Authority Required – telephone/online					
Clinical criteria					
Patient must have received treatment with this drug for this condition prior to [PBS listing date]					
AND					
Clinical criteria					
The treatment must be in conjunction with dietary therapy and exercise,					
AND					
Clinical criteria					
Patient must have had symptomatic atherosclerotic cardiovascular disease prior to starting non-PBS-subsidised treatment with this drug for this condition					
AND					
Clinical criteria					
Patient must have had an LDL cholesterol level in excess of 1.8 mmol per litre prior to starting non-PBS-subsidised treatment with this drug for this condition					

Public Summary Document - March 2023 PBAC Meeting with May 2023 Addendum

AND
Clinical criteria
Patient must have had atherosclerotic disease in two or more vascular territories (coronary, cerebrovascular or peripheral vascular territories) prior to starting non-PBS-subsidised treatment with this drug for this condition; OR
Patient must have had severe multi-vessel coronary heart disease defined as at least 50% stenosis in at least two large vessels prior to starting non-PBS-subsidised treatment with this drug for this condition; OR
Patient must have had at least two major cardiovascular events (i.e. myocardial infarction, unstable angina, stroke or unplanned revascularisation) in the previous 5 years prior to starting non-PBS-subsidised treatment with this drug for this condition; OR
Patient must have had diabetes mellitus with microalbuminuria prior to starting non-PBS-subsidised treatment with this drug for this condition; OR
Patient must have had diabetes mellitus and be aged 60 years or more prior to starting non-PBS-subsidised treatment with this drug for this condition; OR
Patient must be an Aboriginal or Torres Strait Islander with diabetes mellitus that was present prior to starting non-PBS-subsidised treatment with this drug for this condition; OR
Patient must have had a Thrombolysis in Myocardial Infarction (TIMI) risk score for secondary prevention of 4 or higher prior to starting non-PBS-subsidised treatment with this drug for this condition.
AND
Clinical criteria
Patient must have been treated with the maximum recommended dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily) according to the TGA-approved Product Information or the maximum tolerated dose of atorvastatin or rosuvastatin for at least 12 consecutive weeks in conjunction with dietary therapy and exercise prior to initiating non-PBS-subsidised treatment with this drug for this condition; OR
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
Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information
AND
Clinical criteria
Patient must have been treated with ezetimibe for at least 12 consecutive weeks in conjunction with a statin (if tolerated), dietary therapy and exercise prior to initiating non-PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria
<i>Patient must not be receiving concomitant PBS-subsidised treatment with a monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9) for this PBS indication.</i>
AND
Treatment criteria:
Must be treated by a specialist physician; OR
Must be treated by a physician who has consulted a specialist physician.
Prescriber instructions:
<i>Monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9) medications are evolocumab or alirocumab</i>
Prescriber instructions:
<i>Symptomatic atherosclerotic cardiovascular disease is defined as:</i>
<i>(i) the presence of symptomatic coronary artery disease (prior myocardial infarction, prior revascularisation procedure, angina associated with demonstrated significant coronary artery disease (50% or greater stenosis in 1 or more coronary arteries on imaging), or positive functional testing (e.g. myocardial perfusion scanning or stress echocardiography); or</i>
<i>(ii) the presence of symptomatic cerebrovascular disease (prior ischaemic stroke, prior revascularisation procedure, or transient ischaemic attack associated with 50% or greater stenosis in 1 or more cerebral arteries on imaging); or</i>
<i>(iii) the presence of symptomatic peripheral arterial disease (prior acute ischaemic event due to atherosclerosis, prior revascularisation procedure, or symptoms of ischaemia with evidence of significant peripheral artery disease (50% or greater stenosis in 1 or more peripheral arteries on imaging)).</i>

Public Summary Document - March 2023 PBAC Meeting with May 2023 Addendum

The qualifying LDL cholesterol level must have been measured following at least 12 consecutive weeks of combined treatment with a statin, ezetimibe, dietary therapy and exercise (unless treatment with a statin is contraindicated, or following completion of statin trials as described in these prescriber instructions in the event of clinically important adverse events) must be stated at the time of application, documented in the patient's medical records and must have been no more than 8 weeks old at the time non-PBS-subsidised treatment with this drug for this condition was initiated.

A clinically important product-related adverse event is defined as follows:

- (i) Severe myalgia (muscle symptoms without creatine kinase elevation) which is proven to be temporally associated with statin treatment; or*
- (ii) Myositis (clinically important creatine kinase elevation, with or without muscle symptoms) demonstrated by results twice the upper limit of normal on a single reading or a rising pattern on consecutive measurements and which is unexplained by other causes; or*
- (iii) Unexplained, persistent elevations of serum transaminases (greater than 3 times the upper limit of normal) during treatment with a statin.*

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) unless there is a contraindication (e.g. prior rhabdomyolysis) to the alternative statin. This retrial should occur after a washout period of at least 4 weeks, or if the creatine kinase (CK) level is elevated, retrial should not occur until CK has returned to normal.

In the event of a trial of the 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 recommended or maximum tolerated dose has been reached or target LDL-c has been achieved.

One of the following must be stated at the time of application and documented in the patient's medical records regarding prior statin treatment:

- (i) the patient was treated with atorvastatin 80 mg or rosuvastatin 40 mg or the maximum tolerated dose of either for 12 consecutive weeks; or*
- (ii) the doses, duration of treatment and details of adverse events experienced with trials of each atorvastatin and rosuvastatin; or*
- (iii) the patient is contraindicated to treatment with a statin as defined in the TGA-approved Product Information.*

One or more of the following must be stated at the time of application and documented in the patient's medical records regarding the presence of cardiovascular disease or high risk of experiencing a cardiovascular event:

- (i) atherosclerotic disease in two or more vascular territories (coronary, cerebrovascular or peripheral vascular territories); or*
- (ii) severe multi-vessel coronary heart disease defined as at least 50% stenosis in at least two large vessels; or*
- (iii) history of at least two major cardiovascular events (i.e. myocardial infarction, unstable angina, stroke or unplanned revascularisation) in the previous 5 years; or*
- (iv) diabetes mellitus with microalbuminuria; or*
- (v) diabetes mellitus and age 60 years or more;*
- (vi) Aboriginal or Torres Strait Islander with diabetes mellitus; or*
- (vii) a Thrombolysis in Myocardial Infarction (TIMI) risk score for secondary prevention of 4 or higher*

Prescribing instruction:

A patient may qualify for PBS-subsidised treatment under this restriction once only

Prescribing instruction:

For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria

14.2 Flow-on changes are required to prevent the concomitant use of inclisiran with the PCSK9 inhibitors and to allow the switching of treatment to inclisiran from evolocumab (PBS item numbers: 11484K, 11985T, 11986W, 11485L) and alirocumab (PBS item numbers: 12607M, 12608N, 12604J, 13613W).

To prevent the concomitant use of drugs –

1. Add the following criteria to the evolocumab (11485L, 11484K) and alirocumab (12613W, 12604J) initial and grandfather restrictions:

Patient must not be receiving concomitant PBS-subsidised treatment with any of: (i) another monoclonal antibody inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9), (ii) inclisiran, for this PBS indication.

2. Change the following criteria the in the evolocumab (11985T, 11986W) and alirocumab (12607M, 12608N) continuing restrictions:

From: Patient must not be receiving concomitant PBS-subsidised treatment with another drug that belongs to the same pharmacological class as this drug.

To: Patient must not be receiving concomitant PBS-subsidised treatment with *any of: (i) another drug that belongs to the same pharmacological class as this drug, (ii) inclisiran, for this PBS indication.*

To allow switching between drugs change the treatment phase for evolocumab (11985T, 11986W) and alirocumab (12608N, 12607M):

From: **Treatment phase:** Continuing treatment with this drug or switching treatment from another drug within the same pharmacological class.

To: **Treatment phase:** Continuing treatment with this drug or switching treatment from *any of: (i) another drug that belongs to the same pharmacological class as this drug, (ii) inclisiran*

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

15 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

16 Sponsor's Comment

The sponsor had no comment.