5.03 BEMPEDOIC ACID, Tablet 180 mg, Nexletol®, BEMPEDOIC ACID WITH EZETIMIBE Tablet 180 mg bempedoic acid with 10 mg ezetimibe Nexlizet®, Seqirus (Australia) Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested an Authority Required (STREAMLINED) listing for bempedoic acid, as monotherapy and in combination with ezetimibe, for the treatment of adult patients with hypercholesterolaemia (heterozygous familial (HeFH) and non-familial) at high risk of a first cardiovascular (CV) event or with established symptomatic atherosclerotic cardiovascular disease (ASCVD) who have statin intolerance or are on maximally tolerated statin therapy, and despite treatment with ezetimibe, continue to have low-density lipoprotein cholesterol (LDL) levels greater than 1.8 mmol/L.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus best supportive care.

Table 1: Key components of the clinical issue addressed in the submission (as stated in the submission)

Component	Description
Population	Adults with hypercholesterolaemia (heterozygous familial and non-familial) with LDL levels >1.8 mmol/L despite treatment with ezetimibe, who are either at high risk for a cardiovascular event (high risk primary prevention) or have established symptomatic ASCVD (secondary prevention), with a history of statin intolerance or who are receiving maximally tolerated statin therapy.
Intervention	Bempedoic acid 180 mg once daily, orally, as adjunct to standard of care. Fixed-dose combination of bempedoic acid 180 mg and ezetimibe 10 mg once daily, as adjunct to standard of care.
Comparator	Placebo as a proxy for standard of care.
Outcomes	Reduction in LDL leading to a reduction in major cardiovascular events (e.g. cardiovascular death, myocardial infarction, stroke, coronary revascularisation procedures, hospitalisation for unstable angina); adverse events.
Clinical claim	Bempedoic acid is superior to standard of care alone at reducing the risk of MACE, with an inferior but manageable safety profile.

Source: Table 1.1.1, p32 of the submission.
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL, low-density lipoprotein; MACE, major adverse cardiovascular event

2 Background

Registration status

2.1 The submission was made under the TGA/PBAC Parallel Process. At the time of the Sub-Committees consideration, the first and second round Clinical Evaluation Reports

for bempedoic acid and for the fixed dose combination (FDC) of bempedoic acid and ezetimibe were available. The TGA Delegate's overview was received on 30 June 2026 and the TGA Delegate's decision was expected on 18 September 2026.

2.2 The draft Australian therapeutic indication for bempedoic acid is as follows:

- Adults with primary hypercholesterolaemia (heterozygous familial and nonfamilial) or mixed dyslipidaemia, as an adjunct to diet:
  - In combination with a statin or statin with other lipid-lowering therapies in patients unable to reach low-density lipoprotein cholesterol (LDL-C) 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, or for whom a statin is contraindicated.
- Adults with established or at high risk for atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:
  - In patients on a maximum tolerated dose of a statin with or without ezetimibe, or
  - Alone or in combination with ezetimibe in patients who are statin-intolerant, or for whom a statin is contraindicated.

2.3 The draft Australian therapeutic indication for the FDC of bempedoic acid and ezetimibe is as follows:

- Adults with primary hypercholesterolaemia (heterozygous familial and nonfamilial) or mixed dyslipidaemia, as an adjunct to diet:
  - In combination with a statin in patients unable to reach low-density lipoprotein cholesterol (LDL-C) goals with the maximum tolerated dose of a statin in addition to ezetimibe, or
  - Alone in patients who are either statin-intolerant, or for whom a statin is contraindicated, and are unable to reach LDL-C goals with ezetimibe alone, or
  - In patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without a statin.
- Adults with established or at high risk for atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:
  - In patients on a maximum tolerated dose of a statin and not adequately controlled with additional ezetimibe treatment, or
  - In patients who are either statin-intolerant, or for whom a statin is contraindicated, and not adequately controlled with ezetimibe treatment, or
  - In patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without a statin.

2.4 At the time of PBAC consideration, the Module 3 evaluations for the two applications had not yet concluded. There was also an outstanding issue from the Module 4 evaluation of bempedoic acid and ezetimibe FDC. Subject to the resolution of the

outstanding issues, the Delegate was of the mind to approve the registration of both medicines.

2.5 Bempedoic acid and the FDC of bempedoic acid and ezetimibe were approved by the European Medicines Agency in April 2020 for hypercholesterolaemia and mixed dyslipidaemia, and extended to cardiovascular disease risk reduction in May 2024, with the same wording as the proposed TGA indications above.

2.6 Bempedoic acid and the FDC of bempedoic acid and ezetimibe received initial FDA approval in February 2020 as an adjunct to diet, in combination with other LDL lowering therapies, or alone when concomitant LDL lowering therapy is not possible, to reduce LDL in adults with primary hyperlipidaemia, including HeFH. A cardiovascular risk reduction indication was added in March 2024, to reduce the risk of myocardial infarction (MI) and coronary revascularisation in adults who are unable to take recommended statin therapy (including those not taking a statin) with: established cardiovascular disease; or a high risk for a cardiovascular disease event but without established cardiovascular disease.

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

3 Requested listing

3.1 The submission proposed 14 separate restrictions: initiation and continuation restrictions for both high risk primary prevention and secondary prevention for non-familial hypercholesterolaemia, and initiation and continuation restrictions for HeFH, for both bempedoic acid alone and the FDC of bempsedoic acid and ezetimibe. The restrictions for the FDC of bempedoic acid and ezetimibe for each population are identical to the restrictions for bempedoic acid, with the exception of the criterion allowing for patients to be eligible on the basis of contraindications necessitating withdrawal of ezetimibe, which has been removed. The restriction for patients with HeFH applies to both the high risk primary and secondary prevention settings.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
BEMPEDOIC ACID					
Initial treatment					
Bempedoic acid 180 mg tablet, 30	$[redacted]	1	30	5	Nexletol
Bempedoic acid 180 mg with ezetimibe 10 mg tablet, 30	$[redacted]	1	30	5	Nexlizet
Continuing treatment					
Bempedoic acid 180 mg tablet, 30	$[redacted]	1	30	5	Nexletol
Bempedoic acid 180 mg with ezetimibe 10 mg tablet, 30	$[redacted]	1	30	5	Nexlizet

Restriction Summary / Treatment of Concept
Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: Medical Practitioners *Nurse Practitioners*
Restriction type: Authority Required (Streamlined) [new code]

Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply**.**
Episodicity: blank
Severity: blank
Condition: ~~High-risk primary prevention~~ *Non-familial hypercholesterolaemia*
Indication: Non-familial hypercholesterolaemia
Treatment Phase Initial treatment
Clinical criteria:
The treatment must be in conjunction with dietary therapy and exercise,
AND
Clinical criteria:
Patient must have symptomatic atherosclerotic cardiovascular disease; OR
Patient must be at high risk of a cardiovascular event; OR
Patient must identify as Aboriginal or Torres Strait Islander.
AND
Clinical criteria:
Patient must have an LDL cholesterol level in excess of 1.8 millimoles 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*; or
Patient must have developed clinically important product-related adverse event/contraindication as defined in the TGA approved Product Information necessitating withdrawal of ezetimibe
Prescribing 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)).
Prescribing Instructions: *High cardiovascular risk is defined as an estimated risk of a cardiovascular event of at least 10% over 5 years.*
Prescribing Instructions: 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 documented in the patient's medical records and must be no more than 8 weeks old.
Prescribing Instructions: 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.
Prescribing Instructions: 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.
Prescribing Instructions: 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.
Prescribing Instructions: One of the following must be 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 Instructions: Patients with symptomatic atherosclerotic cardiovascular disease where LDL cholesterol cannot be measured due to hypertriglyceridaemia, may qualify under this authority application if they have a non-HDL in excess of 2.4 millimoles per litre.
Restriction Summary / Treatment of Concept
Episodicity: blank
Severity: blank
Condition: ~~High-risk primary prevention~~ *Non-familial hypercholesterolaemia*
Indication: Non-familial hypercholesterolaemia
Treatment Phase Continuing treatment
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

~~**Name, Restriction, Manner of administration and form**~~		~~**Max. Amount**~~	~~**№.of Rpts**~~	~~**Proprietary name**~~	~~**Manufacturer**~~
~~Bempedoic acid 180 mg, orally once daily, tablet~~		~~1~~	~~5~~	~~NEXLETOL®~~	~~Esperion Therapeutics~~
~~Category / Program:~~	~~General Schedule~~				
~~Prescriber type:~~	~~Medical Practitioners~~				
~~Condition:~~	~~Symptomatic atherosclerotic cardiovascular disease~~				
~~PBS Indication:~~	~~Non-familial hypercholesterolaemia~~				
~~Treatment phase:~~	~~Initiation~~				
~~Restriction:~~	~~Authority required (STREAMLINED)~~				
~~Treatment criteria:~~	~~–~~				
~~Clinical criteria:~~	• ~~The treatment must be in conjunction with dietary therapy and exercise,~~ ~~**AND**~~				

	• ~~Patient must have symptomatic atherosclerotic cardiovascular disease,~~ ~~**AND**~~ • ~~Patient must have an LDL cholesterol level in excess of 1.8 millimoles per litre,~~ ~~**AND**~~ • ~~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**~~ • ~~Patient must have been treated with ezetimibe for at least 12 consecutive weeks in conjunction with a statin (if tolerated), OR~~ • ~~Patient must have developed clinically important product-related adverse event/contraindication as defined in the TGA-approved Product Information necessitating withdrawal of ezetimibe.~~
~~Notes:~~	~~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)).~~
	~~Patients with symptomatic atherosclerotic cardiovascular disease where LDL cholesterol cannot be measured due to hypertriglyceridaemia, may qualify under this authority application if they have a non HDL in excess of 2.4 millimoles per litre.~~

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
BEMPEDOIC ACID					
bempedoic acid 180 mg tablet, 30	NEW	1	30	5	Nexletol
Restriction Summary: NEW3 / Treatment of Concept: NEW3a					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: Medical Practitioners *Nurse Practitioners*					
Restriction type: Authority Required (Streamlined) [new code]					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Episodicity: blank					
Severity: blank					
Condition: *Familial heterozygous* Hypercholesterolaemia					
Indication: Familial heterozygous hypercholesterolaemia					

Treatment Phase Initial treatment
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:
Patient must have an LDL cholesterol level in excess of 1.8 millimoles 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*; *or*
Patient must have developed clinically important product-related adverse event/contraindication as defined in the TGA approved Product Information necessitating withdrawal of ezetimibe
Prescribing Instructions: *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, documented in the patient's medical records and must be no more than 8 weeks old.*
Prescribing Instructions: *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.*
Prescribing Instructions: *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.*
Prescribing Instructions: *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.*
Prescribing Instructions: The following must be 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
Prescribing Instructions:

One of the following must be 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: Patients with symptomatic atherosclerotic cardiovascular disease where LDL cholesterol cannot be measured due to hypertriglyceridaemia, may qualify under this authority application if they have a non-HDL in excess of 2.4 millimoles per litre.
Restriction Summary: NEW4 / Treatment of Concept: NEW4a
Indication: *Familial heterozygous hypercholesterolaemia*
Treatment Phase *Continuing treatment*
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

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
BEMPEDOIC ACID + EZETIMIBE					
bempedoic acid 180 mg + ezetimibe 10 mg tablet, 30	NEW	1	30	5	Nexlizet 180/10

Restriction Summary NEW5/ Treatment of Concept: NEW5a
Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: Medical Practitioners *Nurse Practitioners*
Restriction type: Authority Required (Streamlined) [new code]
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply**.**
Episodicity: blank
Severity: blank
Condition: ~~High-risk primary prevention~~ *Non-familial hypercholesterolaemia*
Indication: Non-familial hypercholesterolaemia
Treatment Phase Initial treatment
Clinical criteria:
The treatment must be in conjunction with dietary therapy and exercise,
AND
Clinical criteria:
Patient must have symptomatic atherosclerotic cardiovascular disease; OR
Patient must be at high risk of a cardiovascular event; OR
Patient must identify as Aboriginal or Torres Strait Islander.
AND
Clinical criteria:
Patient must have an LDL cholesterol level in excess of 1.8 millimoles 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.
Prescribing 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)).*
Prescribing Instructions: *High cardiovascular risk is defined as an estimated risk of a cardiovascular event of at least 10% over 5 years.*
Prescribing Instructions: *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 documented in the patient's medical records and must be no more than 8 weeks old.*
Prescribing Instructions: *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.*
Prescribing Instructions: *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.*
Prescribing Instructions: *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.*
Prescribing Instructions: *One of the following must be 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 Instructions:

Patients with symptomatic atherosclerotic cardiovascular disease where LDL cholesterol cannot be measured due to hypertriglyceridaemia, may qualify under this authority application if they have a non-HDL in excess of 2.4 millimoles per litre.
Restriction Summary: NEW2 / Treatment of Concept: NEW2a
Episodicity: blank
Severity: blank
Condition: ~~High-risk primary prevention~~ *Non-familial hypercholesterolaemia*
Indication: Non-familial hypercholesterolaemia
Treatment Phase Continuing treatment
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

~~**Name, Restriction, Manner of administration and form**~~	~~**Max. Amount**~~	~~**№.of Rpts**~~	~~**Proprietary name**~~	~~**Manufacturer**~~
~~Bempedoic acid 180 mg / ezetimibe 10 mg, orally once daily, tablet~~	~~1~~	~~5~~	~~NEXLIZET™~~	~~Esperion Therapeutics~~
~~Category / Program:~~	~~General Schedule~~			
~~Prescriber type:~~	~~Medical Practitioners~~			
~~Condition:~~	~~Symptomatic atherosclerotic cardiovascular disease~~			
~~PBS Indication:~~	~~Non-familial hypercholesterolaemia~~			
~~Treatment phase:~~	~~Initiation~~			
~~Restriction:~~	~~Authority required (STREAMLINED)~~			
~~Treatment criteria:~~	~~–~~			
~~Clinical criteria:~~	~~• The treatment must be in conjunction with dietary therapy and exercise,~~ ~~**AND**~~ ~~• Patient must have symptomatic atherosclerotic cardiovascular disease,~~ ~~**AND**~~ ~~• Patient must have an LDL cholesterol level in excess of 1.8 millimoles per litre,~~ ~~**AND**~~ ~~• 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**~~ ~~• Patient must have been treated with ezetimibe for at least 12 consecutive weeks in conjunction with a statin (if tolerated), dietary therapy and exercise.~~				

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
BEMPEDOIC ACID + EZETIMIBE					
bempedoic acid 180 mg + ezetimibe 10 mg tablet, 30	NEW	1	30	5	Nexlizet 180/10

Restriction Summary NEW5/ Treatment of Concept: NEW5a
Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: Medical Practitioners *Nurse Practitioners*
Restriction type: Authority Required (Streamlined) [new code]
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply**.**
Episodicity: blank
Severity: blank
Condition: *Familial heterozygous* Hypercholesterolaemia
Indication: Familial heterozygous hypercholesterolaemia
Treatment Phase Initial treatment
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:
Patient must have an LDL cholesterol level in excess of 1.8 millimoles 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.
Prescribing Instructions: *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, documented in the patient's medical records and must be no more than 8 weeks old.*
Prescribing Instructions: *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.*
Prescribing Instructions: *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.
Prescribing Instructions: *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.*
Prescribing Instructions: *The following must be 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*
Prescribing Instructions: *One of the following must be 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: *Patients with symptomatic atherosclerotic cardiovascular disease where LDL cholesterol cannot be measured due to hypertriglyceridaemia, may qualify under this authority application if they have a non-HDL in excess of 2.4 millimoles per litre.*
Restriction Summary: NEW4 / Treatment of Concept: NEW4a
Indication: *Familial heterozygous hypercholesterolaemia*
Treatment Phase *Continuing treatment*
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

3.2 The requested PBS restriction for bempedoic acid is narrower than the proposed TGA indication as it includes specific LDL thresholds, ASCVD risk factors and prior therapy requirements (including specific definitions of statin intolerance).

3.3 The proposed PBS restriction for the high risk primary prevention population was based on the recently updated PBS restriction for dapagliflozin for type 2 diabetes (December 2024), which defines high risk of a cardiovascular event based on a risk of at least 10% over 5 years calculated using the Australian Absolute Cardiovascular Disease Risk Calculator or based on patients being of Aboriginal or Torres Strait Islander ancestry. In comparison, methods to determine high risk primary prevention patients in the key bempedoic acid clinical trial (CLEAR OUTCOMES) included Reynolds Risk Scores >30% or Systematic Coronary Risk Evaluation Scores >7.5% over 10 years, coronary artery calcium (CAC) scores >400 Agatston units at any time, or patients with type 1 or type 2 diabetes, aged >65 years (women) or >60 years (men). The Sub-Committees noted that the definition of high risk population in the proposed restriction was also broader than for PCSK9 inhibitors, which applies a different risk criterion for Aboriginal and Torres Strait Islander populations, but was consistent with the PBS listing of dapagliflozin and Closing the Gap strategies. Overall, the Sub-Committees considered that the proposed definition may be appropriate for

bempedoic acid. The Sub-Committees and the evaluation noted that it was unclear whether the populations classified as high risk in the key trial would be representative of those captured by the proposed PBS restriction.

3.4 The definitions of maximally tolerated statins and statin intolerance in the proposed restrictions were based on the PBS restrictions for evolocumab. Definitions of statin intolerance in the requested restriction (specific, documented, clinically important product-related adverse events necessitating withdrawal of a statin treatment to trials each of atorvastatin and rosuvastatin; or contraindicated to treatment with a statin) are more strict than the eligibility criteria of the CLEAR OUTCOMES clinical trial, which specified patient-reported statin intolerance due to an adverse event resulting in the inability to tolerate 2 or more statins at any dose, or 1 statin at any dose and unwilling to attempt a second statin or advised by a physician not to attempt a second statin. Patients in the CLEAR OUTCOMES trial were permitted to be treated with a very low statin dose (lower than minimum recommended doses) during the trial. The evaluation noted that the impact of this difference is unclear. While the proposed PBS definitions of statin intolerance are stricter than the trial eligibility criteria, the application of these criteria in clinical practice is uncertain. The Sub-Committees considered that the application of these criteria in clinical practice was likely to be influenced by how strictly statin intolerance was defined in the restriction. For instance, some patients may be reluctant to trial a second statin if they have not tolerated a first, particularly for primary prevention patients, whereas secondary prevention patients may be more willing. The Sub-Committees considered there was a risk of use beyond the proposed definitions.

3.5 The submission stated that the requirement for patients to have been treated with ezetimibe [and maximally tolerated statins] prior to initiation of bempedoic acid is reflective of previous PBAC decision making in this therapeutic area, whereby patients should be treated with effective lower priced products first. The submission acknowledged that most of the trials included in the bempedoic acid study program did not require prior ezetimibe use but argued that the efficacy of bempedoic acid as a subsequent treatment was supported by the CLEAR TRANQUILITY trial which included a run-in phase requiring patients to be treated with ezetimibe for 4 weeks prior to randomisation, as well as subgroup analyses of other trials demonstrating that prior ezetimibe use is not a treatment effect modifier for bempedoic acid efficacy.

3.6 The submission stated that the proposed LDL threshold of 1.8 mmol/L is consistently recognised in international guidelines as a clinically meaningful target for patients at high or very high cardiovascular risk, particularly in secondary prevention, and identifies patients with unmet clinical need who remain at high residual risk for cardiovascular events, and who are unlikely to reach guideline-recommended targets with lifestyle interventions and conventional therapies alone. The submission noted that the threshold of 1.8 mmol/L is currently used in the PBS restrictions for PCSK9 therapies. The Sub-Committees noted that the proposed PBS population (statin intolerant or receiving maximally tolerated statin therapy, with LDL >1.8 mmol/L despite ezetimibe use) is substantially different to the population in the key

cardiovascular outcomes trial (statin intolerant patients only, with LDL ≥2.6 mmol/L with or without background lipid lowering therapy). While the submission provided evidence of LDL lowering applicable to the broader PBS population in the supportive trials, it has not quantified the cardiovascular risk reductions in this population (see paragraph 6.36), which is likely to have a lower cardiovascular risk than the key trial population and therefore lower absolute benefits of treatment. The Pre-Sub Committee Response (PSCR) acknowledged that the proposed PBS population is broader than the population enrolled in the CLEAR OUTCOMES trial. However, the PSCR argued that an LDL threshold of 2.6 would not be consistent with international clinical guidelines and previous decision making for evolocumab that use 1.8 as a target for patients at high CV risk. The PSCR also noted that LDL is not the only criteria for evaluating risk in CV disease (e.g. diabetes) and noted that the PBS restriction also requires patients to be at a high risk of a CV event. The PSCR considered other risk factors could potentially leave patients with LDL levels between 1.8 and 2.6 mmol/L at a similar risk to patients above 2.6 mmol/L. The PSCR acknowledged that this risk was uncertain. The Sub-Committees noted that LDL ≤1.8 mmol/L is in line with treatment thresholds in clinical guidelines and is consistent with the PBS restrictions of other third line agents for hypercholesteremia (i.e. evolocumab and inclisiran). The Sub-Committees also noted that based on clinical guidelines, for established ASCVD or very high ASCVD risk, the LDL target is <1.4 mmol/L or a ≥50% reduction from baseline, whichever results in the lower level. However, the Sub-Committees noted that the magnitude of CV risk reduction at lower LDL levels remains unquantified and considered that the incremental gains were likely to attenuate with broader use, particularly among patients receiving statins or among patients with a lower baseline risk.

3.7 The submission stated that the continuation criteria for all bempedoic acid restrictions were based on the continuation restriction for evolocumab, which ensures that patients, including those being treated with a statin and ezetimibe (unless contraindicated), remain eligible for ongoing treatment, and ensures that bempedoic acid is used as adjunctive therapy alongside established lipid-lowering strategies to optimise cardiovascular risk reduction. The proposed continuation criteria require patients to have previously received PBS subsidised treatment with bempedoic acid and in conjunction with dietary therapy and exercise. The proposed continuation restriction does not specify requirements for ongoing statin or ezetimibe use (unless contraindicated) alongside bempedoic acid.

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

4 Population and disease

4.1 Hypercholesterolaemia is a common condition, experienced by approximately 8.4% of Australians (ABS 2023), and characterised by elevated serum cholesterol levels, primarily excessive LDL. The causes of hypercholesterolaemia can include both genetic and environmental factors. The vast majority of patients with hypercholesterolaemia

have elevated cholesterol levels in the absence of any specific genetic disorder, developing due to an underlying susceptibility and/or secondary risk factors, including a diet high in saturated fats, sedentary lifestyle, obesity, and smoking[1]. A minority of patients have an autosomal genetic disorder that affects receptor-mediated uptake of LDL, 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). Patients with familial hypercholesterolaemia are exposed to elevated cholesterol levels from birth and typically have very high LDL levels and early onset of atherosclerotic disease. HeFH is one of the most common inherited conditions with an estimated prevalence of 1 in 300 in Australia, however only up to 20% of Australians living with HeFH have been diagnosed (Australian Atherosclerosis Society 2026).

4.2 Hypercholesterolaemia is associated with the development of ASCVD and an increased incidence of MI, stable or unstable angina, coronary revascularisation procedures, stroke, transient ischaemic attack, carotid endarterectomy and intermittent claudication of peripheral arteries. These cardiovascular events can have a major impact on survival, quality of life and future risk of further cardiovascular events.

4.3 Bempedoic acid is an oral, first-in class, adenosine triphosphate (ATP)-citrate lyase (ACL) inhibitor that lowers LDL by inhibiting hepatic cholesterol synthesis. By inhibiting ACL, bempedoic acid reduces the conversion of citrate to acetyl-CoA, an essential substrate for both cholesterol and fatty acid synthesis in the liver. Bempedoic acid targets the same cholesterol biosynthetic pathway as statins but acts at an earlier enzymatic step.

4.4 The submission positioned bempedoic acid as a new treatment option for primary prevention in high-risk patients with non-familial hypercholesterolaemia and LDL >1.8 mmol/L despite treatment with ezetimibe and maximally tolerated statin therapy (or no statin if intolerant).

4.5 In the secondary prevention setting, bempedoic acid was positioned as a new treatment option for patients who are ineligible for PCSK9 inhibitors under current PBS restrictions, and as an add-on treatment option for 'ultra-high risk' patients eligible for PCSK9 inhibitors with LDL >1.8 mmol/L requiring additional LDL lowering (e.g. to a target of <1.4 mmol/L or <1.0 mmol/L).

4.6 For patients with HeFH, the submission positioned bempedoic acid as a new treatment option for high risk primary prevention in patients who are currently ineligible for

[1] Heart, stroke and vascular disease: Australian facts. Web Report. (2026) Available at: https://www.aihw.gov.au/reports/heart-stroke-vascular-diseases/hsvd-facts/contents/risk-factors

PCSK9 inhibitors, who have LDL >1.8 mmol/L and <5.0 mmol/L despite treatment with ezetimibe and maximally tolerated statin therapy (or no statins if intolerant). In patients with HeFH who are already eligible for PCSK9 inhibitors due to very high LDL levels (>5.0 mmol/L) or symptomatic ASCVD, the submission positioned bempedoic acid as add-on therapy in conjunction with other lipid lowering therapies.

4.7 The Sub-Committees considered that the proposed place in therapy was likely reasonable and noted that bempedoic acid would bridge a gap in clinical practice for patients who are on subtherapeutic treatment and unable to reach LDL targets, but who are ineligible for PCSK9 inhibitors.

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

5 Comparator

5.1 The submission nominated placebo as the main comparator as a proxy for standard of care management (ezetimibe monotherapy or ezetimibe in combination with maximally tolerated statin dose). The main justification in support of this nomination was the claim that bempedoic acid will be used as an add-on to standard of care therapies. The Sub-Committees considered that this was reasonable.

5.2 The submission stated that the clinical place in therapy for ezetimibe is well established and the positioning of bempedoic acid after ezetimibe is consistent with its likely use in clinical practice and is consistent with the UK NICE recommended place in therapy (bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia, NICE Committee Papers, March 2020).

5.3 The submission argued against the inclusion of PCSK9 inhibitors as comparators. The submission acknowledged that patients eligible for PCSK9 inhibitors in the secondary prevention setting (and also patients with HeFH for primary prevention) would also technically be eligible for bempedoic acid under the requested PBS restriction, but argued that this would represent a small proportion of expected bempedoic acid use, that PCSK9 inhibitors would likely continue to be the preferred treatment option over bempedoic acid in this setting, and a comparison between bempedoic acid and PCSK9 inhibitors would not be informative. The submission included input from key opinion leaders that use of bempedoic acid would be favoured in secondary prevention patients who have either failed treatment or are unable to reach target LDL cholesterol levels with PCSK9 inhibitors or for those who are unable (contraindicated) or unwilling (due to patient preference) to use them.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer inputs

6.2 The PBAC noted and welcomed the input from health care professionals (7) and medical/consumer organisations (7) via the Office of Health Technology Assessment Consultation Hub.

6.3 The PBAC noted input from health care professionals expressed strong support for the PBS listing of bempedoic acid. The PBAC noted the input described the current clinical treatment pathway for lowering LDL, in which statins are used as first-line therapy, with ezetimibe and PCSK9 inhibitors used as add-on or second-/third-line options. Health care professionals described an unmet clinical need for additional oral lipid lowering therapies, noting that statin intolerance is a significant clinical challenge, leaving patients with inadequate lipid control and an increased cardiovascular risk. Bempedoic acid was considered to address a treatment gap, particularly for high-risk primary prevention patients, patients with established ASCVD, and other patients who require further LDL lowering but are not eligible for injectable therapies under the current PBS criteria. The input noted that patients may prefer oral therapy to injections, and that bempedoic acid may provide a lower-cost option than PCSK9 inhibitors. The input referred to evidence from the CLEAR OUTCOMES trial, which showed fewer cardiovascular events with bempedoic acid than placebo in statin-intolerant patients. The input noted bempedoic acid was well tolerated and did not present the muscle-related adverse events which were associated with statin discontinuation, while noting a need for caution in patients with gout or diabetes.

6.4 The PBAC noted input from Heart Support Australia, Australasian Stroke Academy, Advara HeartCare, FH Australia, Hearts4Heart, Australian Atherosclerosis Society and The Australian & New Zealand Stroke Organisation supported the PBS listing of bempedoic acid as an additional oral lipid-lowering option. The input emphasised an unmet clinical need for patients who remain at increased cardiovascular risk due to inadequate LDL control, particularly those with statin intolerance, which was described as a major clinical issue that can limit treatment options. Bempedoic acid was considered to also help address a treatment gap for patients requiring further LDL reduction who are not eligible for PCSK9 inhibitors under current PBS criteria. The input also identified other benefits associated with bempedoic acid, including its oral administration, a potential cost advantage relative to PCSK9 inhibitors, favourable tolerability, and evidence from the CLEAR OUTCOMES trial showing fewer cardiovascular events with bempedoic acid than placebo in statin-intolerant patients.

Clinical trials

6.5 The submission was based primarily on one head-to-head cardiovascular outcomes trial comparing bempedoic acid plus standard of care to placebo plus standard of care in adult patients with ASCVD (secondary prevention) or at high risk for ASCVD (primary prevention), who were statin intolerant (CLEAR OUTCOMES; N=13,970). Evidence

from the key trial was supported by 4 additional head-to-head trials comparing lipid outcomes for bempedoic acid versus placebo in adults with uncontrolled hypercholesterolaemia in mixed populations with varying levels of background lipid lowering therapies (CLEAR HARMONY, CLEAR WISDOM, CLEAR SERENITY, CLEAR TRANQUILITY), and one head-to-head trial of bempedoic acid with ezetimibe FDC versus bempedoic acid alone, ezetimibe alone or placebo (Ballantyne 2020) in patients at high risk of cardiovascular disease due to ASCVD, HeFH or multiple cardiovascular disease risk factors.

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
CLEAR OUTCOMES	A randomized, double-blind, placebo-controlled study to assess the effects of bempedoic acid (ETC-1002) on the occurrence of major cardiovascular events in patients with, or at high risk for, cardiovascular disease who are statin intolerant. (NCT02993406)	Clinical Study Report, 26 April 2023.
	Nissen SE, Lincoff AM, Brennan D, *et al*. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients.	*N Engl J Med* 2023; 388(15): 1353-64.
	Nissen SE, Menon V, Nicholls SJ, *et al*. Bempedoic acid for primary prevention of cardiovascular events in statin-intolerant patients.	*JAMA* 2023a;330(2):131-40.
	Bays HE, Bloedon L, Brennan D, *et al*. Bempedoic acid for prevention of cardiovascular events in people with obesity: a CLEAR outcomes subset analysis.	*J Am Heart Assoc* 2025; 14(4):e037898.
	Laufs U, Lincoff AM, Nicholls SJ, *et al*. Characteristics and outcomes of patients with and without statin-associated muscle symptoms treated with bempedoic acid in the CLEAR Outcomes trial.	*J Clin Lipidol* 2025; 19(2):337-47.
	Lincoff AM, Ray KK, Sasiela WJ, *et al*. Comparative cardiovascular benefits of bempedoic acid and statin drugs.	*J Am Coll Cardiol* 2024;84(2):152-62.
	Ray KK, Nicholls SJ, Li N, *et al*. Efficacy and safety of bempedoic acid among patients with and without diabetes: prespecified analysis of the CLEAR Outcomes randomised trial.	*Lancet Diabetes Endocrinol* 2024; 12(1):19-28.
	Ridker PM, Lei L, Louie MJ, *et al*. Inflammation and cholesterol as predictors of cardiovascular events among 13 970 contemporary high-risk patients with statin intolerance.	*Circulation* 2024;149(1):28-35.
CLEAR HARMONY	A randomized, double-blind, placebo-controlled, multicenter long-term safety and tolerability study of ETC-1002 in patients with hyperlipidaemia at high cardiovascular risk who are not adequately controlled by their lipid-modifying therapy.	Clinical Study Report, 21 December 2018.
	A randomized, double-blind, placebo-controlled, multicenter long-term safety and tolerability study of ETC-1002 in patients with hyperlipidaemia at high cardiovascular risk who are not adequately controlled by their lipid-modifying therapy. Available at: https://clinicaltrials.gov/study/NCT02666664	Clinicaltrials.gov record NCT02666664.
	Ray KK, Bays HE, Catapano AL, *et al*. Safety and efficacy of bempedoic acid to reduce LDL cholesterol.	*N Engl J Med* 2019; 380(11):1022-32.
	Ridker PM, Lei L, Ray KK, *et al*. Effects of bempedoic acid on CRP, IL-6, fibrinogen and lipoprotein (a) in patients with residual inflammatory risk: a secondary analysis of the CLEAR HARMONY trial.	*J Clin Lipidol* 2023; 17(2):297-302.
CLEAR WISDOM	A long-term, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy of bempedoic acid (ETC-1002) in patients with hyperlipidemia at high cardiovascular risk not adequately controlled by their lipid-modifying therapy.	Clinical Study Report, 7 January 2019.

Trial ID	Protocol title/ Publication title	Publication citation
	A long-term, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy of bempedoic acid (ETC-1002) in patients with hyperlipidemia at high cardiovascular risk not adequately controlled by their lipid-modifying therapy. Available at: https://clinicaltrials.gov/study/NCT02991118	Clinicaltrials.gov record NCT02991118.
	Goldberg AC, Leiter LA, Stroes ES, *et al*. Effect of bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease: the CLEAR WISDOM randomized clinical trial.	*JAMA* 2019; 322(18):1780-8.
CLEAR SERENITY	A randomized, double-blind, parallel group, multicenter study to evaluate the efficacy and safety of bempedoic acid (ETC-1002) 180 mg compared to placebo added to background lipid-modifying therapy in patients with elevated LDL-C who are statin intolerant.	Clinical Study Report, 11 December 2018.
	A randomized, double-blind, parallel group, multicenter study to evaluate the efficacy and safety of bempedoic acid (ETC-1002) 180 mg compared to placebo added to background lipid-modifying therapy in patients with elevated LDL-C who are statin intolerant. Available at: https://clinicaltrials.gov/study/NCT02988115	Clinicaltrials.gov record NCT02988115.
	Laufs U, Banach M, Mancini GJ, *et al*. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance.	*J Am Heart Assoc* 2019; 8(7):e011662.
CLEAR TRANQUILITY	A randomized, double-blind, placebo-controlled, parallel group, multicenter study to evaluate the efficacy and safety of bempedoic acid (ETC-1002) 180 mg/day as add-on to ezetimibe therapy in patients with elevated LDL-C on low dose or less than low dose statins.	Clinical Study Report, 18 January 2019.
	A randomized, double-blind, placebo-controlled, parallel group, multicenter study to evaluate the efficacy and safety of bempedoic acid (ETC-1002) 180 mg/day as add-on to ezetimibe therapy in patients with elevated LDL-C. Available at: https://clinicaltrials.gov/study/NCT03001076	Clinicaltrials.gov record NCT03001076.
	Ballantyne CM, Banach M, Mancini GJ, Lepor NE, Hanselman JC, Zhao X, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: a randomized, placebo-controlled study.	*Atherosclerosis* 2018; 277:195-203.
Ballantyne 2020	A randomized, double-blind, parallel group study to evaluate the efficacy and safety of bempedoic acid 180 mg + ezetimibe 10 mg fixed dose combination compared to bempedoic acid, ezetimibe, and placebo alone in patients treated with maximally tolerated statin therapy.	Clinical Study Report, 8 January 2019.
	A randomized, double-blind, parallel group study to evaluate the efficacy and safety of bempedoic acid 180 mg + ezetimibe 10 mg fixed dose combination compared to bempedoic acid, ezetimibe, and placebo alone in patients treated with maximally tolerated statin therapy. Available at: https://clinicaltrials.gov/study/NCT03337308.	Clinicaltrials.gov record NCT03337308.
	Ballantyne CM, Laufs U, Ray KK, *et al*. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy.	*Eur J Preventive Cardiol* 2020; 27(6):593-603.

Source: Table 2.2.1, pp84-86 of the submission.

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

Table 3: Key features of the included evidence

Trial	Design / duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
CLEAR OUTCOMES N=13,970	R, DB, MC Median 3.4 years	Low	Statin intolerant adults with uncontrolled non-familial hypercholesterolaemia (LDL ≥2.6 mmol/L) in primary or secondary prevention settings.	Time to first occurrence: MACE-4 (CV death, non-fatal MI, non-fatal stroke, or coronary revascularisation); MACE-3 (CV death, non-fatal MI, or non-fatal stroke); disaggregated cardiovascular endpoints, safety.	Patient characteristics, circumstances of use and cardiovascular event incidence
CLEAR HARMONY N=2,230	R, DB, MC 52 weeks	Low	Adults with uncontrolled familial/non-familial hypercholesterolaemia (LDL ≥1.8 mmol/L) on maximally tolerated statin therapy in the secondary prevention setting.	Safety, LDL change from baseline	Not used
CLEAR WISDOM N=779	R, DB, MC 52 weeks	Low	Statin intolerant adults with uncontrolled familial/non-familial hypercholesterolaemia (LDL ≥3.4 mmol/L (primary prevention population) or LDL ≥2.6 mmol/L (secondary prevention population) at first screening visit, and ≥1.8 mmol/L for both groups at second screening visit).	LDL change from baseline, safety	Not used
CLEAR SERENITY N=345	R, DB, MC 24 weeks	Low	Statin intolerant adults with uncontrolled hypercholesterolaemia (LDL ≥2.6 mmol/L for patients taking ezetimibe 10 mg daily prior to first screening visit, or LDL ≥3.1 mmol/L for patients not taking ezetimibe at first screening visit, and ≥1.8 mmol/L for both groups at second screening visit) in either primary or secondary prevention settings.	LDL change from baseline, safety	Not used

Trial	Design / duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
CLEAR TRANQUILITY N=269	R, DB, MC 12 weeks	Low	Statin intolerant adults with uncontrolled hypercholesterolaemia (LDL ≥2.6 mmol/L for patients taking ezetimibe 10 mg daily prior to first screening visit, or LDL ≥3.1 mmol/L for patients not taking ezetimibe at first screening visit, and ≥1.8 mmol/L for both groups at second screening visit) in either primary or secondary prevention settings.	LDL change from baseline, safety	Not used
Ballantyne 2020 N=382 N=301 *post hoc* efficacy population [a]	R, DB, MC 12 weeks	Unclear	Adults with uncontrolled familial/non-familial hypercholesterolaemia (LDL ≥2.6 mmol/L for secondary/HeFH population; LDL ≥3.4 mmol/L for primary population) on maximally tolerated statin therapy in either primary or secondary prevention setting.	LDL change from baseline, safety	Not used

Source: Table 2.2.2, p89; Table 2.3.1, pp92-93 of the submission.
Abbreviations: DB, double blind; LDL, low density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MC, multi-centre; R, randomised.
[a] The submission noted data integrity concerns in Ballantyne (2020), where 51 patients reported treatment adherence but had no detectable study drug at Week 12. These patients were predominantly from three study sites in a single metropolitan area, which together enrolled 21.2% of the population. Due to these concerns, data from these sites were excluded, and *post hoc* efficacy and safety analyses were conducted on the remaining sample (n=301; 78.8% of the full analysis set).

6.8 Data integrity concerns in Ballantyne (2020), affecting 51 patients (mainly from three sites), led to exclusion of these sites and *post hoc* analyses in the reduced population (n=301; 78.8%).

6.9 Baseline patient and disease characteristics from the key CLEAR OUTCOMES trial were well balanced between treatment arms. Overall, participants were predominantly male (52%) and white (91%), with a mean age of 65 years. The trial capped enrolment of primary prevention patients at 30% of the overall patient population. All patients were classed as statin intolerant, with the majority of patients (78%) having failed at least 2 statins. Background lipid therapies were statins (23%, almost all on a very low dose), ezetimibe (12%), and other lipid modifying therapies (7%); however, the majority of patients had no concomitant lipid modifying therapies at baseline (59%). Mean baseline LDL was 3.6 mmol/L, and median LDL was 3.5 mmol/L (range 0.7 to 11.9 mmol/L).

6.10 Patients in the primary prevention subgroup were slightly older than those in the secondary prevention subgroup (67.9 years versus 64.5 years) and included a greater proportion of females (59.0% versus 43.6%). Approximately 64.7% of primary prevention patients had a history of diabetes (one of the three possible primary prevention eligibility criteria), compared to 33.4% in the secondary prevention group.

6.11 The 5 supportive trials from the CLEAR trial program included adults with hypercholesterolaemia, with or without documented ASCVD and/or HeFH (diagnosed by genotyping or clinical assessment). Two of the supportive trials enrolled statin

intolerant patients, requiring a documented history of prior statin use, with adverse events experienced during statin therapy that improved or resolved when the statin was discontinued or dose reduced (CLEAR SERENITY, CLEAR TRANQUILITY). The 3 remaining trials (CLEAR HARMONY, CLEAR WISDOM, Ballantyne 2020) enrolled patients receiving maximally tolerated statin therapy, with doses determined by investigators based on their medical judgement and local standard of care, and which could include regimens other than daily dosing, including no to very low doses. Baseline characteristics were generally well balanced between treatment arms for each trial.

6.12 Mean baseline LDL levels in the supportive trials ranged from 2.7 mmol/L (CLEAR HARMONY) to 4.1 mmol/L (CLEAR SERENITY). The submission suggested the differences in baseline LDL levels in the included trials may be due to differences in prior LDL cholesterol lowering medications. However, the baseline LDL inclusion criteria also differed between trials, with only one trial (CLEAR HARMONY) specifying a single LDL threshold of ≥1.8 mmol/L prior to randomisation. All other trials enrolled patients with higher LDL levels of ≥2.6 to ≥3.4 mmol/L either at randomisation, or at a previous screening visit. The Sub-Committees noted that the higher initial LDL thresholds resulted in trial populations that may not be representative of patients with lower LDL cholesterol levels in the requested Australian population.

Comparative effectiveness

6.13 Results for the primary outcome of CLEAR OUTCOMES, time to first occurrence of MACE-4 and incidence of disaggregated components, are summarised in Table 4.

Table 4: Time to first occurrence of 4-component MACE, CLEAR OUTCOMES (Full Analysis Set)

Endpoint	Bempedoic acid (N=6,992)	Placebo (N=6,978)	Hazard Ratio (95% CI)
Composite endpoint – MACE-4			
Number of first events, n (%)	819 (11.7)	927 (13.3)	**0.87 (0.79, 0.96)**
Total number of events / total person years	1,190 / 23,994	1,471 / 23,846	**-**
Total number of events per 100 person years	5.0	6.2	**0.80 (0.72, 0.89)**
MACE-4 disaggregated components, n (%) [% MACE-4 events]			
Non-fatal MI	219 (3.1) [26.7]	293 (4.2) [31.6]	-
Coronary revascularisation	273 (3.9) [33.3]	300 (4.3) [32.4]	-
Non-fatal stroke	108 (1.5) [13.2]	127 (1.8) [13.7]	-
CV death	219 (3.1) [26.7]	207 (3.0) [22.3]	-

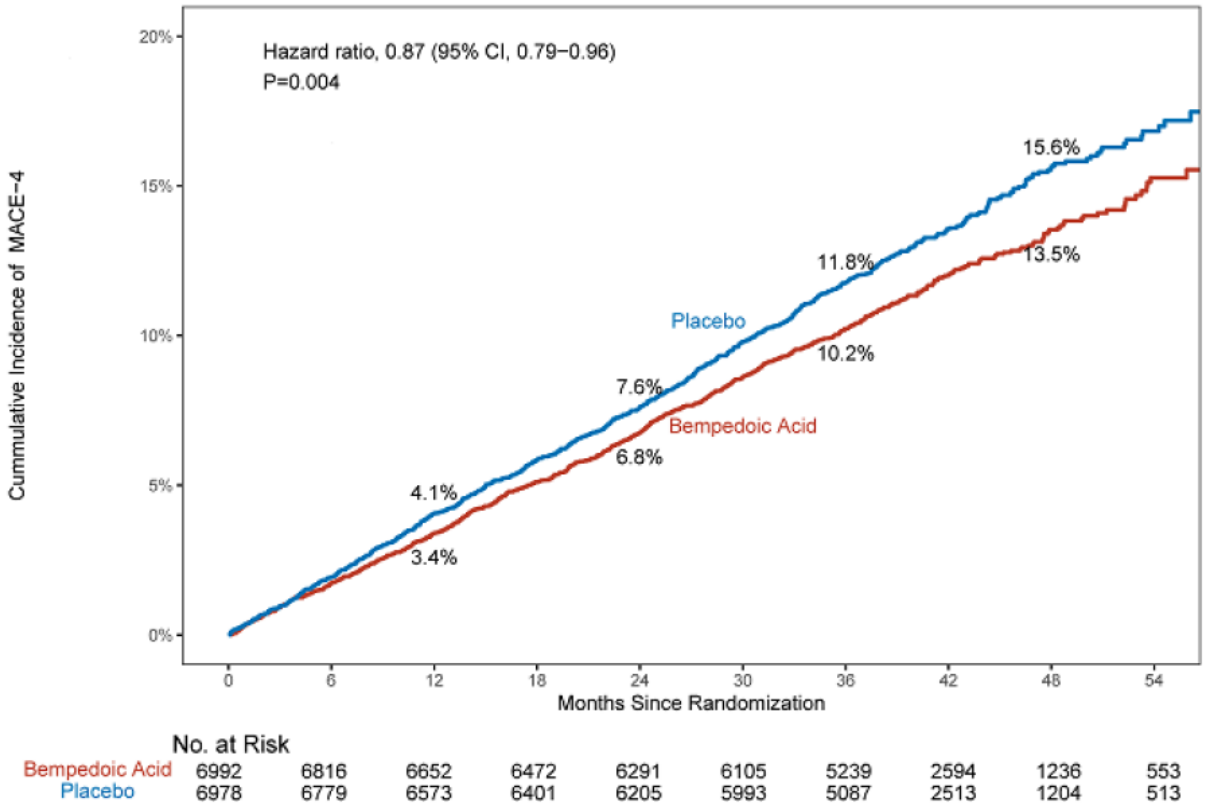
Source: Table 2.5.1, p145 of the submission; Table 25, Table 27, Table 37, CLEAR OUTCOMES clinical study report.
Abbreviations: CI, confidence interval; CV, cardiovascular; MACE-4, 4-point major adverse cardiovascular events; MI, myocardial infarction
Bold indicates statistically significant results.
Note: Median follow-up 3.4 years (range 0 to 5.7 years)
Note: MACE-4 was defined as the composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or coronary revascularisation. The primary endpoint was analysed using a Cox proportional hazards model with treatment as a factor. The hazard ratio and its 95% CI and p-value from the log-rank test were provided. Total patient years were calculated by summing across all patients' total number of days from the date of randomisation to the last date of event or censoring for the endpoint and dividing by 365.25. Hazard ratios, 95% CI and p-values were estimated by Andersen-Gill mean intensity model, with robust sandwich estimates of the covariance matrix.

6.14 Over a median follow-up of 3.4 years, bempedoic acid had a statistically significantly lower risk of a first event of cardiovascular death, non-fatal MI, non-fatal stroke or

coronary revascularisation compared to placebo (hazard ratio [HR] 0.87; 95% CI 0.79, 0.96).

6.15 The cumulative risk of a MACE-4 was lower for the bempedoic acid group within the first year of treatment, and by Year 3 the difference between treatment arms represented an absolute reduction of 1.6%, which increased to 2.0% by Year 5. The incidence of MACE-4 was 5 events per 100 person-years in the bempedoic acid arm compared to 6.2 events per 100 person-years in the placebo arm. Figure 1 presents a Kaplan-Meier plot of cumulative incidence of MACE-4 in CLEAR OUTCOMES.

Figure 1: Kaplan-Meier plot of cumulative incidence of MACE-4 over time, CLEAR OUTCOMES (FAS)



Source: Figure 2.5.1, p146 of the submission
Abbreviations: CI, confidence interval; FAS, full analysis set; MACE, major adverse cardiovascular event
NOTE: MACE-4 was defined as the composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or coronary revascularisation. Median follow up: 3.4 years (range 0 to 5.7 years). The majority of patients in the bempedoic acid and placebo groups did not have MACE-4 events and completed the study and were censored at the end of study visit (84.3% vs. 82.1%, respectively). Patients who discontinued the study early were censored at early study termination (3.8% vs. 4.4%, respectively) or at the time of study completion due to non-CV death (0.2% in both groups).

6.16 Subgroup analyses of the MACE-4 primary outcome assessed differences by characteristics including sex, race, age, baseline cardiovascular risk category, baseline LDL values, diabetes history, and BMI, with results generally aligned with those for the overall population, and a consistent benefit demonstrated for bempedoic acid over placebo for most subgroups. Cardiovascular disease risk category (primary versus secondary prevention) was the only subgroup analysis with a nominally significant interaction with treatment, with larger relative reductions observed with bempedoic

acid treatment compared to placebo in the primary prevention population compared to the secondary prevention population (p-value for treatment interaction 0.0302).

6.17 The number of patients experiencing any of the disaggregated MACE-4 components as individual outcomes during the trial is summarised in Table 5.

Table 5: Individual event analysis of any of the MACE-4 components, CLEAR OUTCOMES (FAS)

MACE-4 individual event analysis	Bempedoic acid (N=6,992)	Placebo (N=6,978)	Hazard Ratio (95% CI)
Coronary revascularisation	435 (6.2)	529 (7.6)	**0.81 (0.72, 0.92)**
Non-fatal MI	236 (3.4)	317 (4.5)	0.73 (0.62, 0.87)
Non-fatal stroke	119 (1.7)	144 (2.1)	0.82 (0.64, 1.05)
Cardiovascular death	269 (3.8)	257 (3.7)	1.04 (0.88, 1.24)

Source: Table 27, CLEAR OUTCOMES clinical study report.
Abbreviations: FAS, full analysis set; MACE-4, 4-point major adverse cardiovascular events; MI, myocardial infarction
Note: Time to first occurrence for each of the components of MACE-4; patients could be included in more than one category. Statistical significance was assessed for coronary revascularisation as part of hierarchical testing for key secondary outcomes, with all other endpoints assessed after the cessation of hierarchical testing due to non-statistically significant differences for fatal and non-fatal stroke.

6.18 Of the MACE-4 components, a statistically significantly lower risk was noted for coronary revascularisation, and a nominally significantly lower risk for non-fatal MI, while no differences between treatment arms were observed for non-fatal stroke or cardiovascular death. The submission argued that the lack of benefit demonstrated for cardiovascular deaths may reflect the relatively short duration of follow-up, the effectiveness of contemporary adjunctive therapies and insufficient sample size (noting that larger sample sizes are typically required to demonstrate a mortality benefit with non-statin LDL lowering therapies).

6.19 Fewer patients in the bempedoic acid group had multiple MACE-4 compared with the placebo group; second events were experienced by 3.7% and 5.0% of patients in the bempedoic and placebo groups, respectively, with a consistently lower incidence in the bempedoic acid group compared to placebo for each subsequent event. An analysis of total events demonstrated a statistically significantly greater treatment effect for bempedoic acid compared to placebo (HR: 0.80, 95% CI 0.72, 0.89).

6.20 All on-study deaths were adjudicated by the clinical events committee to determine if the death was cardiovascular related. When there was no clear non-cardiovascular cause of death documented, the death was adjudicated as undetermined and classified as a cardiovascular death. Overall, 858 patient deaths were recorded (436 in the bempedoic acid arm and 422 in the placebo arm), of which 530 were classed as cardiovascular (271 (62.2% of deaths) and 259 (61.4%), respectively). There were 118 deaths of undetermined cause (43.5% of 271 total cardiovascular deaths) in the bempedoic arm and 94 deaths of undetermined cause (36.3% of 259 cardiovascular deaths) in the placebo arm that were classified as cardiovascular deaths. The submission claimed that observed increases in cardiovascular deaths over time were due to an increase in deaths of undetermined cause coinciding with the COVID-19 pandemic (the trial was conducted from November 2016 to November 2022). A sensitivity analysis that excluded all post-pandemic undetermined CV deaths resulted in a hazard ratio of 0.94 (95% CI 0.76, 1.16) for cardiovascular death, which was consistent with results for the full analysis set.

6.21 Key secondary outcomes in the CLEAR OUTCOMES trial were assessed in hierarchical order, with results presented in Table 6.

Table 6: Key secondary efficacy cardiovascular endpoints from CLEAR OUTCOMES (FAS)

Endpoint	Bempedoic acid (N=6,992)	Placebo (N=6,978)	Hazard Ratio (95% CI)
Composite endpoint – MACE-3			
Number of events, n (%)	575 (8.2)	663 (9.5)	**0.85 (0.76, 0.96)**
Key secondary endpoints			
Fatal and non-fatal MI	261 (3.7)	334 (4.8)	**0.77 (0.66, 0.91)**
Coronary revascularisation	435 (6.2)	529 (7.6)	**0.81 (0.72, 0.92)**
Fatal and non-fatal stroke	135 (1.9)	158 (2.3)	0.85 (0.67, 1.07)
CV death	269 (3.8)	257 (3.7)	1.04 (0.88, 1.24)
All-cause mortality	434 (6.2)	420 (6.0)	1.03 (0.90, 1.18)
Other secondary efficacy endpoints			
Non-fatal MI, non-fatal stroke, coronary revascularisation or all-cause mortality	962 (13.8)	1,062 (15.2)	0.89 (0.82, 0.97)
MACE-5	831 (11.9)	952 (13.6)	0.86 (0.78, 0.94)
Non-fatal MI	236 (3.4)	317 (4.5)	0.73 (0.62, 0.87)
Fatal MI	29 (0.4)	21 (0.3)	1.38 (0.79, 2.42)
Non-fatal stroke	119 (1.7)	144 (2.1)	0.82 (0.64, 1.05)
Fatal stroke	18 (0.3)	16 (0.2)	1.12 (0.57, 2.20)
Fatal and non-fatal haemorrhagic stroke	20 (0.3)	9 (0.1)	2.21 (1.01, 4.85)
Fatal and non-fatal non-haemorrhagic stroke	118 (1.7)	150 (2.1)	0.78 (0.61, 0.99)
Hospitalisation for unstable angina	91 (1.3)	137 (2.0)	0.66 (0.50, 0.86)
Total event analyses, total events/total person years (total events per 100 person years)			
MACE-3	660/23,994 (2.8)	793/23,845 (3.3)	0.83 (0.73, 0.93)
Coronary revascularisation	530/23,960 (2.2)	678/23,815 (2.8)	0.78 (0.68, 0.89)
Non-fatal MI	264/23,962 (1.1)	379/23,816 (1.6)	0.69 (0.58, 0.83)
Non-fatal stroke	127/23,960 (0.5)	157/23,813 (0.7)	0.80 (0.63, 1.03)

Source: Table 2.5.3, p148; Table 2.5.4, p150 of the submission; Section 2.5.1.1.3, p149 of the submission; Table 40, Table 14.2.6, CLEAR OUTCOMES clinical study report.

Abbreviations: CV, cardiovascular; FAS, full analysis set; MACE-3, 3-point major adverse cardiovascular events; MACE-5, 5-point major adverse cardiovascular events; MI, myocardial infarction

Bold indicates statistically significant results.

Note: Median follow-up 3.4 years (range 0 to 5.7 years)

Note: MACE-3 was a composite endpoint of cardiovascular death, non-fatal MI, or non-fatal stroke. MACE-5 was a composite endpoint of cardiovascular death, non-fatal MI, non-fatal stroke, coronary revascularisation and hospitalisation for unstable angina. Hazard ratios were based on Cox proportional hazards model with treatment as an explanatory variable.

6.22 Over a median follow-up of 3.4 years, treatment with bempedoic acid was associated with a significant reduction in the risk of MACE-3 (cardiovascular death, non-fatal MI, or non-fatal stroke) compared to placebo. Treatment with bempedoic acid was also associated with a statistically significantly lower risk of fatal and non-fatal MI combined, and coronary revascularisation, however no statistically significant differences were found for the secondary outcomes of fatal and non-fatal stroke, cardiovascular death or all-cause mortality.

6.23 Detailed subgroup analyses of cardiovascular endpoints for the primary and secondary prevention patient groups from CLEAR OUTCOMES are summarised in Table 7.

Table 7: Summary of cardiovascular outcomes by primary and secondary prevention subgroups, CLEAR OUTCOMES

Endpoint, n (%)	Primary prevention			Secondary prevention		
	BA (N=2,100)	PBO (N=2,106)	HR (95% CI)	BA (N=4,892)	PBO (N=4,872)	HR (95% CI)
Cardiovascular endpoints						
MACE-4	111 (5.3)	161 (7.6)	0.68 (0.53, 0.87)	708 (14.5)	766 (15.7)	0.91 (0.82, 1.01)
MACE-3	83 (4.0)	134 (6.4)	0.61 (0.46, 0.80)	492 (10.1)	529 (10.9)	0.92 (0.81, 1.04)
MACE-5	112 (5.3)	164 (7.8)	0.69 (0.54, 0.88)	719 (14.7)	788 (16.2)	0.90 (0.81, 0.99)
Non-fatal MI	28 (1.3)	44 (2.1)	0.63 (0.39, 1.01)	208 (4.3)	273 (5.6)	0.75 (0.63, 0.90)
Fatal MI	1 (<0.1)	3 (0.1)	0.33 (0.03, 3.18)	28 (0.6)	18 (0.4)	1.55 (0.86, 2.80)
Coronary revascularisation	50 (2.4)	68 (3.2)	0.73 (0.50, 1.05)	385 (7.9)	461 (9.5)	0.83 (0.72, 0.94)
Non-fatal stroke	26 (1.2)	33 (1.6)	0.78 (0.47, 1.31)	93 (1.9)	111 (2.3)	0.83 (0.63, 1.10)
Fatal stroke	2 (<0.1)	4 (0.2)	0.50 (0.09, 2.75)	16 (0.3)	12 (0.2)	1.33 (0.63, 2.81)
CV death	37 (1.8)	65 (3.1)	0.57 (0.38, 0.85)	232 (4.7)	192 (3.9)	1.20 (0.99, 1.46)
Fatal / non-fatal MI	29 (1.4)	47 (2.2)	0.61 (0.39, 0.98)	232 (4.7)	287 (5.9)	0.80 (0.67, 0.95)
Fatal / non-fatal stroke	27 (1.3)	37 (1.8)	0.76 (0.46, 1.26)	108 (2.2)	121 (2.5)	0.89 (0.68, 1.15)
Hospitalisation for UA	10 (0.5)	17 (0.8)	0.58 (0.26, 1.27)	81 (1.7)	120 (2.5)	0.79 (0.60, 1.05)
All-cause mortality	75 (3.6)	109 (5.2)	0.73 (0.54, 0.98)	359 (7.3)	311 (6.4)	1.15 (0.99, 1.34)

Source: Table 2.5.5, Table 2.5.6, p151 of the submission; Table 14.2.1.1.1B, Table 14.2.2.7A, CLEAR OUTCOMES clinical study report.
Abbreviations: BA, bempedoic acid; CV, cardiovascular; HR, hazard ratio; MACE-3, 3-point major adverse cardiovascular events; MACE-4, 4-point major adverse cardiovascular events; MACE-5, 5-point major adverse cardiovascular events; MI, myocardial infarction; PBO, placebo; UA, unstable angina
Note: MACE-4 was defined as the composite endpoint of CV death, non-fatal MI, non-fatal stroke, or coronary revascularisation. MACE-3 was defined as the composite endpoint of CV death, non-fatal MI, or non-fatal stroke. MACE-5 was defined as composite endpoint of CV death, non-fatal MI, non-fatal stroke, coronary revascularisation, or hospitalisation for unstable angina. Median follow-up: 3.4 years (range: 0-5.7 years).

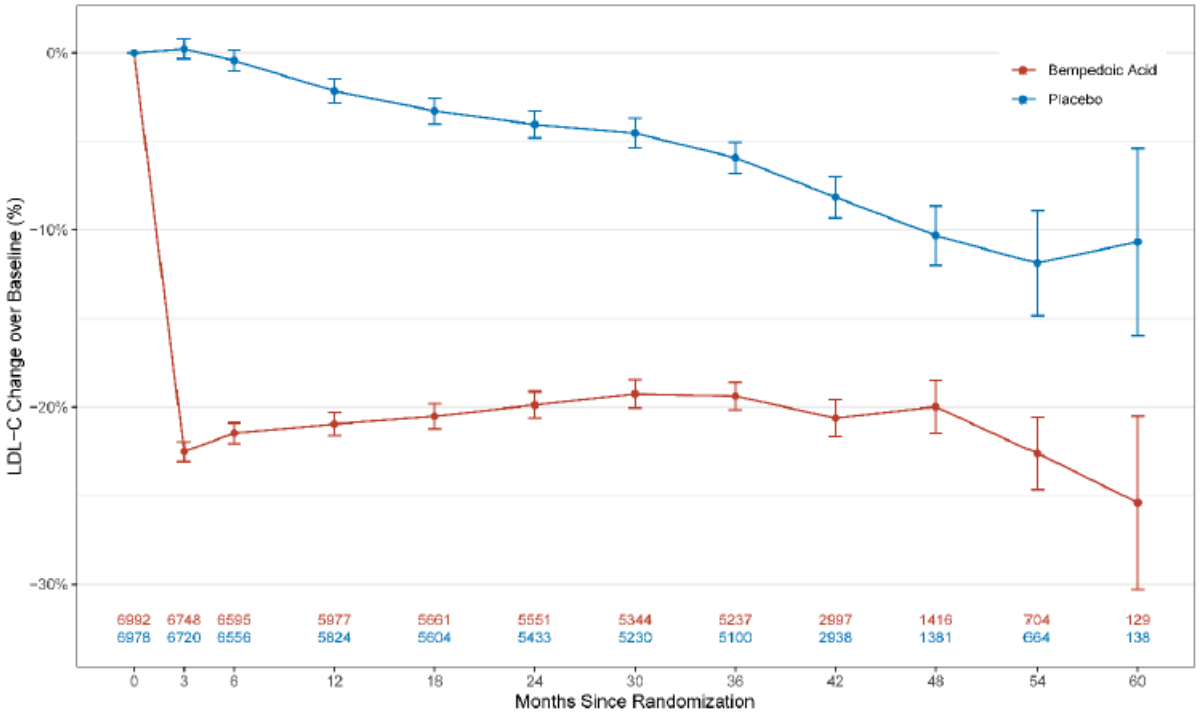
6.24 While fewer MACE-4, MACE-3, and component events were observed with bempedoic acid than with placebo in both subgroups, hazard ratios for all endpoints were numerically lower in the primary prevention subgroup compared with the secondary prevention subgroup. The trial investigators noted that this difference did not appear to be related to observed differences between the populations, with patient disposition generally consistent between the subgroups and no differences in baseline characteristics that would be sufficient to explain the difference in risk of MACE. However, a comparison of baseline characteristics indicated a numerically lower proportion of males, higher baseline age and a substantially higher proportion of patients with diabetes in the primary prevention population (41.0% male, average age 68 years, 66.1% with diabetes) compared to the secondary prevention population (56.3% male, average age 64.5 years, 36.8% with diabetes). This difference was likely driven by the inclusion of diabetes (in women aged >65 years or men aged >60 years) as an eligibility criterion for the primary prevention subgroup.

6.25 The trial investigators noted that the numerical difference in risk of MACE-4 between primary and secondary prevention patients appeared to be driven largely by the risk of cardiovascular death, with bempedoic acid associated with a lower estimated hazard ratio (HR 0.57; 95% CI 0.38, 0.85) in primary prevention patients compared to secondary prevention patients (HR 1.20; 95% CI 0.99, 1.46). Similar to the overall trial population, sensitivity analyses were conducted that removed cardiovascular deaths adjudicated with an undetermined cause that occurred during the COVID-19

pandemic, which resulted in differences between the primary and secondary prevention populations that were consistent with the main analysis (primary prevention: HR 0.40; 95% CI 0.22, 0.74; secondary prevention HR 1.07; 95% CI 0.85, 1.34).

6.26 Change in LDL over time in CLEAR OUTCOMES is summarised in Figure 2.

Figure 2: Percent change from baseline in LDL cholesterol over time through end of study, CLEAR OUTCOMES (FAS)



Source: Figure 11, CLEAR OUTCOMES clinical study report
Abbreviations: CI, confidence interval; LDL-C, low-density lipoprotein cholesterol

6.27 In CLEAR OUTCOMES, treatment with bempedoic acid had an immediate impact on LDL levels with nominally significant between-treatment differences noted for percentage change from baseline at 3 months (least squares mean % difference -22.7; 95% CI -23.5, -22.0), with LDL levels remaining consistently lower in the bempedoic acid arm compared to placebo over time. However, the between-treatment difference lessened at later time points, with the trial investigators suggesting this may be due to the effect of initiation or intensification of background lipid modifying therapies, which occurred with greater frequency in the placebo group (15.6%) compared to the bempedoic acid group (9.4%); or due to treatment discontinuations in the bempedoic acid arm (29.1%). An evaluation of the effect of treatment in the absence of initiation or intensification of background lipid modifying therapies resulted in lower proportional changes in LDL from baseline in both treatment arms.

6.28 Change from baseline to Month 6 in LDL in the overall trial population and by primary and secondary prevention subgroups is summarised in Table 8.

Table 8: Change from baseline in LDL at 6 months by overall trial population and by primary and secondary prevention subgroups, CLEAR OUTCOMES (FAS)

Subgroup	Treatment arm	LDL, mmol/L, mean (SD)			mean % change from baseline (SD)	LS mean difference in % change (95% CI)
		Baseline	Endpoint	Absolute change from baseline		
Overall population	BA (n=6,992)	3.6 (0.9)	2.8 (0.9)	-0.8 (0.9)	-21.7 (23.9)	-21.1 (-21.9, -20.3)
	PBO (n=6,978)	3.6 (0.9)	3.5 (1.1)	-0.1 (0.8)	-0.6 (24.7)	
Primary prevention	BA (n=2,100)	3.7 (0.9)	2.8 (0.9)	-0.9 (0.9)	-22.7 (23.2)	-21.3 (-22.7, -20.0)
	PBO (n=2,106)	3.7 (0.9)	3.6 (1.1)	-0.1 (0.8)	-1.4 (22.0)	
Secondary prevention	BA (n=4,892)	3.6 (0.9)	2.8 (1.0)	-0.8 (0.9)	-21.3 (24.2)	-21.0 (-22.0, -20.0)
	PBO (n=4,872)	3.6 (0.9)	3.5 (1.1)	-0.1 (0.8)	-0.2 (25.8)	

Source: Table 14.2.3.2.4; Table 14.2.3.2.3B, CLEAR OUTCOMES clinical study report.
Abbreviations: BA, bempedoic acid; LDL, low-density lipoprotein; PBO, placebo; SD, standard deviation
Note: LS Means and 95% CI are based on ANCOVA with percent change from baseline; placebo-corrected. Subgroup analyses were performed on LDL reduction using the FAS based on observed data (i.e., no imputation performed).

6.29 Changes from baseline to Month 6 in LDL were consistent between the primary and secondary prevention populations in CLEAR OUTCOMES. The trial investigators noted that comparable LDL changes in each subgroup were also observed at subsequent time points during the trial.

6.30 Results for change in LDL cholesterol from baseline to the end of each study for the supportive trials are summarised in Table 9.

Table 9: Change from baseline in LDL at the longest available endpoint of the included trials

Trial and endpoint	Treatment arm	LDL, mmol/L, mean (SD)			LS mean % change from baseline (SE)	LS mean difference in % change (95% CI)
		Baseline	Endpoint	Absolute change from baseline		
CLEAR HARMONY (Week 52)	BA (n=1,488)	2.7 (0.7)	2.3 (0.8)	-0.4 (0.7)	-12.6 (0.7)	**-13.6 (-15.8, -11.3)**
	PBO (n=742)	2.6 (0.8)	2.6 (0.9)	-0.01 (0.7)	1.0 (0.9)	
CLEAR WISDOM (Week 52)	BA (n=522)	3.1 (1.0)	2.6 (0.9)	-0.5 (0.9)	-13.2 (1.4)	**-12.3 (-16.8, -7.7)**
	PBO (n=257)	3.2 (1.0)	3.0 (1.0)	-0.2 (1.0)	-1.0 (1.8)	
CLEAR SERENITY (Week 24)	BA (n=234)	4.1 (1.0)	3.2 (1.0)	-1.0 (0.9)	-21.2 (1.4)	**-18.9 (-23.0, -14.9)**
	PBO (n=111)	4.0 (1.0)	3.9 (1.0)	-0.1 (0.7)	-2.3 (1.6)	
CLEAR TRANQUILITY (Week 12)	BA (n=181)	3.4 (0.8)	2.5 (1.0)	-0.9 (0.9)	-23.5 (1.9)	**-28.5 (-34.4, -22.5)**
	PBO (n=88)	3.2 (0.7)	3.3 (0.8)	0.1 (0.6)	5.0 (2.3)	
Ballantyne 2020 (Week 12)	BA + EZE (n=86)	4.0 (1.1)	2.4 (1.0)	-1.5 (1.1)	-36.2 (2.6)	BA+EZE vs PBO **-38.0 (-46.5, -29.6)** BA+EZE vs BA **-19.0 (-26.1, -11.9)** BA+EZE vs EZE **-13.1 (-19.7, -6.5)**
	BA (n=88)	3.8 (1.0)	3.0 (1.0)	-0.7 (0.9)	-17.2 (2.5)	
	EZE (n=86)	3.9 (1.1)	2.9 (1.0)	-1.0 (0.9)	-23.2 (2.2)	
	PBO (n=41)	4.0 (1.2)	4.0 (1.5)	0.1 (0.9)	1.8 (3.5)	

Source: Table 2.5.7, p152 of the submission; CLEAR trial program clinical study reports.
Abbreviations: BA, bempedoic acid; EZE, ezetimibe; LDL, low-density lipoprotein; LS, least squares; PBO, placebo; SD, standard deviation; SE, standard error
Bold indicates statistically significant results.
Note: LS Means and 95% CI are based on ANCOVA with percent change from baseline; placebo-corrected.

6.31 Treatment with bempedoic acid was associated with statistically significantly larger percentage reductions from baseline in LDL compared to placebo at each trial's

longest endpoint. The effect of bempedoic acid on LDL reduction at the study endpoint appeared to be smaller in the trials of patients on maximally tolerated statins compared to the trials of statin intolerant patients. This difference was also observed at a common time point (12 weeks) across the trials. Treatment with bempedoic acid was associated with an absolute reduction in LDL from baseline of between 0.4 and 1.0 mmol/L (and 1.5 mmol/L for the FDC of bempedoic acid and ezetimibe) at the trials' longest endpoints.

6.32 Ballantyne (2020) reported change from baseline in LDL at week 12 for the FDC of bempedoic acid and ezetimibe compared with placebo and with ezetimibe alone. The comparison against placebo demonstrated the largest between group difference in LDL of -38.0%, reflecting the combined effect of bempedoic acid and ezetimibe when added to maximally tolerated statins. When compared with ezetimibe alone, the FDC demonstrated an additional LDL reduction of 13.1%, representing the incremental effect of adding bempedoic acid to ezetimibe and maximally tolerated statins.

6.33 Subgroup analyses for change from baseline in LDL were performed in the supportive trials, assessing differences by characteristics including sex, race, age, baseline cardiovascular risk category, baseline LDL values, diabetes history, and BMI. Results indicated a consistent trend for LDL lowering in the bempedoic acid treatment groups relative to placebo. While the trials were not powered to show statistical differences between patient subgroups, potential treatment effect modifiers for LDL reduction were identified, including sex (CLEAR HARMONY, CLEAR SERENITY), baseline LDL (CLEAR WISDOM), BMI (CLEAR WISDOM), diabetes (CLEAR SERENITY), and statin use (CLEAR TRANQUILITY). The CLEAR HARMONY, CLEAR WISDOM, CLEAR SERENITY and CLEAR TRANQUILTY trials assessed differences in LDL change by baseline statin intensity or statin/no statin use (Table 10).

Table 10: Change from baseline in LDL at 6 months by statin use or intensity, CLEAR HARMONY, CLEAR WISDOM, CLEAR SERENITY, CLEAR TRANQUILITY

Trial	Baseline statin intensity	LS mean change in LDL from baseline to week 12 (SE), mmol/L		LS mean difference in % change (95% CI)
		BA	PBO	
CLEAR HARMONY	Low	n=95 -19.36 (2.086)	n=45 7.33 (3.631)	-26.69 (-35.04, -18.35)
	Low/Moderate (*post hoc*)	n=706 -18.07 (0.708)	n=362 1.97 (1.202)	-20.04 (-22.78, -17.30)
	Moderate	n=317 -17.87 (0.751)	n=611 1.20 (1.252)	-19.06 (-21.93, -16.20)
	High	n=718 -16.16 (0.692)	n=363 1.29 (1.225)	-17.45 (-20.21, -14.69)
CLEAR WISDOM *(post hoc)*	No statin	n=48 -24.60 (3.638)	n=29 -2.58 (4.373)	-22.02 (-33.40, -10.65)
	Low/moderate	n=179 -14.90 (1.630)	n=89 3.21 (2.115)	-18.11 (-23.38, -12.85)
	High	n=271 -14.43 (1.492)	n=135 2.78 (2.095)	-17.21 (-22.27, -12.14)
CLEAR SERENITY (*post hoc*)	No LMT therapy	n=127 -22.25 (NR)	n=64 -0.14 (NR)	-22.11 (NR)
	No statin (other LMT only)	n=79 -27.84 (NR)	n=33 -4.51 (NR)	-23.33 (NR)
	Very low dose statin	n=18 -15.00 (NR)	n=10 2.36 (NR)	-17.36 (NR)
CLEAR TRANQUILITY	No statin (other LMT only)	n=119 -31.63 (2.077)	n=60 3.11 (2.252)	-34.74 (-40.82, -28.66)
	Low or very low dose statin	n=22 -9.39 (3.357)	n=25 11.13 (5.431)	-20.5 (-33.44, -7.58)

Source: Table 21, CLEAR HARMONY clinical study report; Table 21, CLEAR WISDOM clinical study report; Table 19, CLEAR SERENITY clinical study report; Table 14.2.4.1g, CLEAR TRANQUILITY clinical study report.

Abbreviations: BA, bempedoic acid; EZE, ezetimibe; LDL, low-density lipoprotein; LMT, lipid modifying therapy; LS, least squares; PBO, placebo; SE, standard error

Note: In CLEAR HARMONY and CLEAR WISDOM, low intensity statins included simvastatin 10 mg, pravastatin 10-20 mg, lovastatin 20 mg, fluvastatin 20-40 mg, or pitavastatin 1 mg. Low intensity statins also included those patients taking low-dose statins using an alternative regimen (i.e. every other day or for a specified number of days per week. Moderate intensity statins included atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin 20-40 mg (after a protocol amendment, simvastatin ≥40 mg was not allowed), pravastatin 40-80 mg, lovastatin 40 mg, fluvastatin XL 80 mg, fluvastatin 40 mg, pitavastatin 2-4 mg. High intensity statins included atorvastatin 40-80 mg and rosuvastatin 20-40 mg. CLEAR SERENITY defined very low dose statin therapy as an average daily dose of rosuvastatin <5mg, atorvastatin <10 mg, simvastatin <10 mg, lovastatin <20 mg, pravastatin <40 mg, fluvastatin <40 mg, or pitavastatin 2 mg. CLEAR TRANQUILITY defined low dose statin therapy as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg, and very low statin doses as any amount below the doses defined as low dose above.

6.34 Regardless of background statin intensity, bempedoic acid demonstrated nominally significant reductions in LDL cholesterol compared to placebo at Week 12. However, the between treatment differences in LDL change from baseline appeared to become smaller with increasing intensity of background statin treatment. These results were consistent with findings of a post hoc pooled analysis of the same four trials (Ballantyne 2022), in which the authors observed that the degree of LDL lowering with bempedoic acid was affected by the presence or absence of background statin therapy, with numerically greater reductions in LDL observed for patients not receiving a statin (median -30.40%) compared to those treated with background statins (median -17.93%). The PSCR noted that the Ballantyne 2022 post hoc pooled

analysis also reported that after adjusting for covariates, female sex, a history of diabetes, absence of a baseline statin use, the presence of baseline ezetimibe use and higher hsCRP were associated with achieving at least a 30% reduction in LDL. The PSCR argued that it was likely that only a small minority of bempedoic acid patients will be treated with a high intensity statin whereas nearly all patients will be treated with ezetimibe. Therefore, with respect to background therapy it is more likely for the effect of bempedoic acid to be under, rather than over-estimated across the population as a whole. The Sub-Committees noted that the interaction between bempedoic acid and ezetimibe has been demonstrated in one small trial, however the magnitude of benefit is highly uncertain for the requested population. The Sub-Committees also considered that the proportion of patients likely to be receiving treatment with a high intensity statin was uncertain, particularly given that the proposed restriction specifies that patients receiving a statin must be on the maximum tolerated dose. The Pre-PBAC Response argued that, while the bempedoic acid treatment effect based on the CLEAR OUTCOMES trial may have the potential to be overestimated (due to lack of concomitant statin use) or underestimated (due to lack of concomitant ezetimibe use), it remains the most suitable basis for decision-making.

6.35 The submission argued that the consistent effects of bempedoic acid (and the FDC of bempedoic acid and ezetimibe) on LDL, regardless of differences in the included patient populations, demonstrated that the broader CLEAR trial program can be reasonably extrapolated to predict cardiovascular benefit, consistent with established evidence that proportional reductions in LDL correspond to proportional reductions in cardiovascular events (Nelson 2024).

6.36 The submission included results of a post hoc analysis of CLEAR OUTCOMES, which compared the relationship between LDL reduction and cardiovascular outcomes with that observed in the Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis of statin trials (Lincoff 2024). Using a CTTC-aligned definition of major vascular events and standardising results per 1 mmol/L LDL reduction at 12 months, the analysis found that bempedoic acid was associated with risk reductions comparable to those observed with statins (HR 0.75; 95% CI 0.63, 0.90 versus CTTC rate ratio 0.78; 95% CI 0.76, 0.80). Results were broadly consistent across primary and secondary prevention subgroups, although the primary prevention estimate suggested a larger effect with wider confidence intervals. Reasons for the apparent increased impact of treatment on the primary prevention population are unclear. Lincoff (2024) suggested that patients who are at earlier stages of atherosclerotic disease may experience enhanced treatment effect from LDL reduction with bempedoic acid or statins. The submission argued that these findings support the principle that relative cardiovascular risk reduction is proportional to [absolute] LDL lowering and therefore LDL reductions can be reliably translated into expected MACE reductions in populations where cardiovascular outcomes are not directly measured (i.e., the supportive trials). The evaluation considered that this argument appeared reasonable. However, the submission did not attempt to quantify the expected reductions in

MACE outcomes in the broader PBS population rather than the narrower CLEAR OUTCOMES trial population.

6.37 No quality of life or other patient-reported outcomes were reported in the included trials.

Comparative harms

6.38 Key safety outcomes reported in the CLEAR OUTCOMES trial are summarised in Table 11.

Table 11: Key adverse events in the CLEAR OUTCOMES trial (Safety Analysis Set)

Treatment-emergent adverse event (n,%)	BA (n=7,001)	PBO (n=6,964)
Any adverse event	6,040 (86.3)	5,919 (85.0)
Drug related adverse event	1,438 (20.5)	1,186 (17.0)
Serious adverse event	1,767 (25.2)	1,733 (24.9)
Serious drug related adverse event	43 (0.6)	35 (0.5)
Adverse event leading to discontinuation	759 (10.8)	722 (10.4)
Deaths [a]	165 (2.4)	163 (2.3)
Adverse events of special interest		
Any hepatic enzyme abnormality	407 (5.8)	325 (4.7)
Elevations in hepatic enzymes	317 (4.5)	209 (3.0)
Cholelithiasis-related adverse event	216 (3.1)	152 (2.2)
Creatine kinase laboratory abnormalities	45 (0.6)	40 (0.6)
Any muscle-related adverse event	1,052 (15.0)	1,070 (15.4)
Any new onset diabetes mellitus by baseline glycaemic status (n/N, %):		
- prediabetes	569/2,918 (19.5)	586/2,877 (20.4)
- normoglycaemia	52/938 (5.5)	54/863 (6.3)
- no diabetes	621/3,856 (16.1)	640/3,740 (17.1)
Worsening hyperglycaemia in patients with diabetes	713/3,145 (22.7)	746/3224 (23.1)
Worsening hyperglycaemia in patients with inadequately controlled diabetes	443/1,357 (32.6)	446/1,367 (32.6)
Renal impairment related laboratory abnormalities	3,765 (53.8)	2,978 (42.8)
Renal impairment related adverse events	802 (11.5)	59 (8.6)
Tendinopathy-related adverse event	118 (1.7)	128 (1.8)
Tendon rupture	86 (1.2)	66 (0.9)
Atrial fibrillation	229 (3.3)	246 (3.5)
Malignancy	321 (4.6)	341 (4.9)
Uric acid increase >ULN	3,143 (64.9)	1,819 (37.9)
Hyperuricaemia-related adverse events	1,147 (16.4)	574 (8.2)
Gout	215 (3.1)	143 (2.1)

Source: Table 2.5.9, p156; Table 2.5.10, p158; Table 2.5.11, p160 of the submission.
Abbreviations: BA, bempedoic acid; PBO, placebo; ULN, upper limit of normal
[a] Non-cardiovascular deaths only. All on-study deaths were adjudicated by the CEC and included in the efficacy analysis.

6.39 The proportions of patients reporting treatment emergent adverse events were generally consistent between treatment arms, with the exception of treatment related adverse events which were observed for 20.5% of patients in the bempedoic acid arm and 17.0% in the placebo arm.

6.40 Several predefined adverse events of special interest were monitored during the CLEAR OUTCOMES trial. The overall incidence of hepatic enzyme abnormalities or elevations, cholelithiasis-related adverse events, and renal impairment related

adverse events were numerically higher in the bempedoic acid arm compared to the placebo arm, while the incidence of other events were similar across treatment arms, including muscle-related adverse events and incidence of new onset or worsening diabetes mellitus. Increases in mean serum uric acid levels and incidence of gout were also measured in the trial due to observed uric acid level increases observed in previous bempedoic acid studies. Uric acid increases greater than the upper limit of normal were noted for 64.9% of patients in the bempedoic acid arm compared to 37.9% of the placebo arm, and gout was reported for 3.1% and 2.1% of patients, respectively.

6.41 Safety outcomes in the supportive trials were similar to those reported for CLEAR OUTCOMES, with a higher incidence of adverse events in the trials of longer duration.

Benefits/harms

6.42 On the basis of direct evidence presented in the submission from the CLEAR OUTCOMES trial, for every 1,000 patients with non-familial hypercholesterolaemia, with or without atherosclerotic cardiovascular disease, who are statin-intolerant and have LDL levels ≥2.6 mmol/L, treatment with bempedoic acid in comparison to placebo over a median duration of exposure of 3.4 years would result in:

- Approximately 14 fewer patients with a coronary revascularisation procedure.
- Approximately 11 fewer patients with a non-fatal heart attack.
- No apparent difference in non-fatal stroke.
- No apparent difference in cardiovascular deaths.
- Approximately 21% lower LDL levels after 6 months.
- Approximately 35 additional patients with an adverse event related to their treatment.

Clinical claim

6.43 The submission described bempedoic acid and the FDC of bempedoic acid and ezetimibe as superior in terms of effectiveness and inferior in terms of safety compared to placebo as a proxy for standard of care. The Sub-Committees considered that this therapeutic conclusion proposed by the submission was adequately supported by the evidence presented in the submission. However, it was noted that the following issues should be considered:

- The proposed PBS population (statin intolerant or receiving maximally tolerated statin therapy, with LDL >1.8 mmol/L despite ezetimibe use) is substantially different to the population in the key cardiovascular outcomes trial (statin intolerant patients only, with LDL ≥2.6 mmol/L with or without background lipid lowering therapy). While the submission provided evidence of LDL lowering applicable to the broader PBS population in the supportive trials, it has not quantified the cardiovascular risk reductions in this population, which is likely to have a lower cardiovascular risk than the key trial population and therefore lower absolute benefits of treatment. The Sub-Committees considered that the

magnitude of clinical benefit was likely to attenuate with broader use, particularly among patients receiving statins or among patients with a lower baseline cardiovascular risk.

- The magnitude of benefit associated with the combined use of bempedoic acid and statins is uncertain, given that both treatments share the same inhibitory pathway and data from the supportive trials suggest smaller LDL treatment effects for bempedoic acid with increasing statin intensity. The Sub-Committees noted that regardless of background statin intensity, bempedoic acid demonstrated reductions in LDL compared to placebo. However, the Sub-Committees also noted that LDL reductions decrease with increasing intensity of background statin therapy and the uncertainty regarding the proportion of patients who would receive a high intensity statin in the PBS population makes the magnitude of benefit that would be observed in practice difficult to determine. The Sub-Committees considered that despite the argument from the PSCR (paragraph 6.34), the proportion of patients likely to be treated with a high intensity statin was uncertain, particularly given that the proposed restriction specifies that patients receiving a statin must be on the maximum tolerated dose.
- The submission does not quantify the difference in baseline risk and downstream treatment effects due to different baseline LDL levels for the population with an LDL between 1.8 and 2.6 mmol/L. The Sub-Committees advised that analysis of those with baseline LDL 1.8–2.6 mmol/L from the CLEAR HARMONY trial, presented as ≥2.6 / < 2.6 mmol/L, would have been informative, but data was not available to support this broader population as requested for the PBS listing.

6.44 The PBAC considered that the claim of superior comparative effectiveness was adequately supported by the data, but that the magnitude of benefit for the proposed population was uncertain.

6.45 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.46 The submission presented a stepped economic evaluation of bempedoic acid compared to placebo in statin-intolerant patients with and without pre-existing cardiovascular disease who have an LDL ≥2.6 mmol/L. The submission also presented scenario analyses based on the primary prevention and secondary prevention patient populations. The economic evaluation was based on the CLEAR OUTCOMES trial with additional modelled data. The economic evaluation was presented as a cost effectiveness/cost utility analysis.

6.47 The scope of the economic analysis (bempedoic acid single agent versus placebo in statin intolerant patients with LDL ≥2.6 mmol/L) was substantially narrower than the proposed use of bempedoic acid under the PBS (bempedoic acid single agent and bempedoic acid with ezetimibe FDC versus standard of care in statin intolerant patients or patients using a maximally tolerated statin dose who have an LDL >1.8

mmol/L despite treatment with ezetimibe). The broader PBS population is likely to be at lower risk than the trial population given the differences in required LDL levels and use of background statin therapies but this difference in risk was not quantified in the submission. The PSCR noted that while the CLEAR OUTCOMES trial was conducted at a time when the threshold for cholesterol lowering treatments was higher, recent international guidelines support lower LDL targets and argued that sustained reductions above 1.8 mmol/L provide a clinically proven surrogate outcome for cardiovascular events. The Sub-Committees noted that the key issue relates less to the appropriateness of use in the broader PBS population, but rather the lack of supporting clinical evidence, adequate quantification and economic assessment of including these patients. The Sub-Committees noted that in two published Australian economic models of bempedoic acid LDL reductions observed in clinical trials were translated into cardiovascular event reductions, with absolute benefits determined by the baseline risk of the modelled population[2,3]. The Sub-Committees further noted that the submission for evolocumab quantified the difference in baseline risk and downstream treatment effects due to different baseline LDL levels when requesting an extension of indication for the population with an LDL between 1.8 and 2.6 mmol/L (evolocumab Public Summary Document [PSD], July 2022 PBAC meeting). Overall, the Sub-Committees considered that not adapting the model for use in the broader population (LDL between 1.8 and 2.6 mmol/L and higher statin use) favoured bempedoic acid as applying outcomes from the higher-risk trial population to a broader, lower-risk population overestimates absolute benefits.

6.48 During the evaluation, results for the separate analyses of the primary and secondary prevention populations were preferred over the mixed population given the substantial differences in cardiovascular risk between these two populations. Additionally, the generalisability of the mixed analysis was unclear as the distribution of primary and secondary prevention patients in the overall population (30% primary; 70% secondary) was largely an artifact of the CLEAR OUTCOMES eligibility criteria and may not reflect the distribution in clinical practice. The Sub-Committees agreed with the evaluation that this was appropriate, as they are heterogeneous populations. The Sub-Committees also noted that the 70% secondary/30% primary prevention split was an a priori decision in the trial and was not expected to reflect clinical practice. The Pre-PBAC Response argued that the primary and secondary prevention populations represent a continuum of cardiovascular risk, rather than distinct groups, with the main difference being whether a symptomatic event such as MI, stroke or

[2] Perera K, Kam N, Ademi Z, Liew D, Zomer E. Bempedoic acid for high-risk patients with CVD as adjunct lipid-lowering therapy: A cost-effectiveness analysis. J Clin Lipidol. 2020 Nov-Dec;14(6):772-783.

[3] Morton JI, Liew D, Watts GF, Zoungas S, Nicholls SJ, Dixon P, Ademi Z. Rethinking cardiovascular prevention: cost-effective cholesterol lowering for statin-intolerant patients in Australia and the UK. Eur J Prev Cardiol. 2025 Sep 22;32(13):1259-1270

revascularisation has already occurred. It stated that this was why the pivotal trial combined and analysed the populations together, as their underlying risk was considered similar. The Pre-PBAC Response proposed an alternative weighting of 26% for primary prevention and 74% for secondary prevention, based on estimates derived from the financial estimates.

6.49 Key components of the economic evaluation are summarised in Table 12.

Table 12: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-effectiveness/cost-utility analysis
Outcomes	CV events avoided, life years, quality-adjusted life years
Time horizon	25 years
Methods used to generate results	Markov cohort analysis
Treatments	Single agent bempedoic acid versus placebo
Model structure	Markov cohort analysis with 27 health states including an event-free health state and other health states defined by different combinations of 0, 1 or 2+ prior non-fatal MIs, strokes or coronary revascularisation procedures. Includes 2 death states for CV death and non-CV death. The model also tracks treatment status (on-treatment, off-treatment) and hospitalisations for unstable angina. The Sub-Committees considered that given the need to capture the impact of multiple prior events over time, a microsimulation modelling approach may have been more appropriate.
Cycle length	6 months (with half cycle correction)
Patient characteristics and circumstances of use	Baseline age, sex and the proportion of patients with prior CV disease were based on reported baseline values from the combined treatment arms of the CLEAR OUTCOMES trial. Baseline age and sex were assumed to be the same in the primary and secondary prevention populations. Adherence and persistence to bempedoic acid treatment were based on reported values from the combined treatment arms of the CLEAR OUTCOMES trial. The same patterns of use were assumed in the primary and secondary prevention settings. The Sub-Committees considered that this was reasonable, although the trial data may overestimate adherence (as the trial had a 4 week placebo run-in phase to exclude patients with <80% adherence). The base case analysis did not include the use of bempedoic acid with ezetimibe FDC or other lipid lowering therapies.
Transition probabilities	No treatment discontinuations were assumed to occur during the first 3.5 years of the model (imperfect persistence during this period was captured using a persistence adjustment factor to drug costs). At 4 years, treatment discontinuation was estimated based on the total treatment discontinuations reported in the CLEAR OUTCOMES trial. Treatment discontinuations after this time point were estimated as a constant per-cycle risk derived from the CLEAR OUTCOMES trial. The Sub-Committees considered the modelled treatment discontinuation was overly simplistic, resulting in a poor reflection of expected clinical practice (paragraph 6.52). The submission assumed that patients who discontinue bempedoic acid have the same risk as patients treated with placebo. During the first 3.5 years, event risks for non-fatal CV events (MI, stroke, coronary revascularisation, hospitalisation for unstable angina) were derived from follow-up adjusted incidence rates for each treatment arm of the CLEAR OUTCOMES trial. After 3.5 years, non-fatal CV event risks were adjusted using risk multipliers for age (AIHW Heart, stroke and vascular disease report 2025) and prior event history (Nedkoff 2023, Peng 2022). The Sub-Committees considered that this was appropriate in principle, however agreed with concerns raised by the evaluation related to the use of Nedkoff 2023 and Peng 2022 (paragraphs 6.55–6.57).

Component	Description
	During the first 3.5 years, event risks for CV death were derived from follow-up adjusted incidence rates from the placebo arm of the CLEAR OUTCOMES trial. The submission stated it was appropriate to use placebo arm estimates for both treatment arms as bempedoic acid did not demonstrate a statistically significant reduction in CV mortality during the trial period. The Sub-Committees considered that this was likely reasonable, however also considered that the use of all data (pooled) was likely more appropriate. After this timepoint, cardiovascular death was assumed to only occur due to a fatal MI or fatal stroke. Case fatality rates were estimated based on *post hoc* analyses of data from the placebo arm of the CLEAR OUTCOMES trial that reclassified adjudicated causes of CV death to either MI or stroke. These estimates were then applied as scaling factors to the age-adjusted non-fatal CV event risks for each individual treatment arm to estimate the total risk of each event. Fatal events for each treatment arm were derived by subtracting non-fatal events from the total events. The Sub-Committees noted that this was an unconventional approach which led to implausible patterns of CV deaths over ages (paragraphs 6.60–6.63). Non-CV death event risks for the whole modelled duration were based on age and sex-specific mortality rates derived from Australian life tables in 2021–2023 (ABS, 2024), adjusted to exclude CV deaths based on AIHW data on causes of death in Australia in 2022 (AIHW, 2023).
Utility values	CV health state utility values (event-free: 0.85, history of MI: -0.12, history of stroke: -0.24, history of coronary revascularisation: -0.00) were based on estimates from an Australian cost-effectiveness study of icosapent ethyl versus placebo for the treatment of established CV disease (Gao 2019). The Sub-Committees considered that applying the same utility to the event free health state for both the primary and secondary prevention populations was not appropriate. Patients in the event-free health state were assumed to have the same baseline utility value regardless of prior event history. A multiplicative approach was used to estimate disutility in patients with multiple events. Each event was assumed to have a 6-month duration. The Sub-Committees noted that the multiplicative structure resulted in unusual consequences (such as no effect of additional events beyond the second health event) which resulted in uncertainty. The Sub-Committees also considered that the disutilities appeared high, and that the 6-month figure was unsupported.
Costs	Drug costs were estimated based on the proposed price of single agent bempedoic acid. Health state costs for CV disease were based on values reported in published Australian economic analyses: • Event-free, $5,426 per year (Ademi 2021). • MI, $14,412 + $5,426 = $19,838 per year (Abebe 2025 + event-free costs). • Stroke, $13,525 + $5,426 = $18,951 per year (Abebe 2024 + event-free costs). • Coronary revascularisations, $5,426 per year (same as event-free). Patients in the event-free health state were assumed to have the same disease management costs regardless of prior event history. A hierarchical approach was used to estimate costs in patients with multiple events. Acute event costs for CV death (Abebe 2025), non-fatal MI (Ioannides Demos 2010) and non-fatal stroke (Kim 2024) were based on values reported in published literature. Costs were inflated to 2025 Australian dollars using the AIHW health inflation index. Acute event costs for coronary revascularisation and hospitalisations for unstable angina were estimated based on AR-DRG cost items (National Hospital Cost Data Collection Report, Public Sector Round 25 (2020–2021).

Component	Description
	The Sub-Committees considered that the way in which the costs were applied to the model was highly problematic and led to the costs associated with MI and stoke to be substantially overestimated. The Sub-Committees also noted that acute event costs were based on a range of different sources and should have been based on AR-DRGs to isolate hospitalisation costs and ensure consistency. The Pre-PBAC Response provided a revised economic model with revision to costs (see paragraphs 6.66–6.72).
Discount rate	5% for costs and outcomes
Software package	Microsoft Excel

Source: Table 3.1.1, pp187-188; Section 3.3-3.6, pp205-229 of the submission
Abbreviations: ABS, Australian Bureau of Statistics; AIHW, Australian Institute for Health and Welfare; AR-DRG, Australian Refined Diagnosis Related Groups; CV, cardiovascular; FDC, fixed dose combination; MI, myocardial infarction

6.50 All patients begin the model in the event-free health state regardless of any prior history of cardiovascular events.

6.51 The submission nominated a 25-year time horizon for the economic analysis. The submission claimed that this was consistent with previous PBAC considerations of lipid lowering therapies for cardiovascular disease (evolocumab July 2022; icosapent ethyl November 2023).

6.52 During the first 3.5 years of the model, patients can experience a non-fatal cardiovascular event (MI, stroke, unstable angina, coronary revascularisation), cardiovascular death or non-cardiovascular death in each 6-month cycle. After 3.5 years, the allowable transitions change and patients can discontinue therapy, experience a non-fatal cardiovascular event, experience a fatal MI or fatal stroke (grouped together as cardiovascular death) or die due to non-cardiovascular causes in each 6-month cycle. The Sub-Committees considered the modelled treatment discontinuation was overly simplistic, resulting in a poor reflection of expected clinical practice. The Sub-Committees considered that treatment discontinuation should be higher initially and higher in primary prevention versus secondary prevention. Assuming no treatment discontinuation for the initial 3.5 years of the model was not appropriate. The Sub-Committees noted that increasing the treatment discontinuation in the extrapolated period increased the incremental cost-effectiveness ratio (ICER) by [redacted]%. The Sub-Committees considered this sensitivity analysis was an improvement but remained insufficient. The Pre-PBAC Response argued that the model's trial-derived outcomes are intrinsically linked to the discontinuation rate observed in the trial, such that changing the discontinuation rate would make the model inconsistent with the evidence base on which it was built. The Pre-PBAC Response noted that the model is sensitive to discontinuation in the extrapolated period because the treatment effect is based on the trial ITT population, which was diluted by 30% of patients who discontinued treatment. In the model, patients who discontinue immediately stop receiving any treatment effect, further reducing the overall benefit in the bempedoic acid arm; therefore, higher discontinuation rates produce greater dilution of the treatment effect.

6.53 Non-fatal MI, stroke and coronary revascularisation procedures are associated with both transient (acute) impacts as well as ongoing (chronic) impacts. Hospitalisation for unstable angina is assumed to have an acute impact only. The post-event history is tracked using specific health states defined by different combinations of 0, 1 or ≥2

prior non-fatal MIs, strokes or coronary revascularisation procedures. Patients experiencing more than 2 events of the same type would incur the acute costs and disutilities associated with the event but remain in the same health state. Patients can experience up to 4 different non-fatal cardiovascular events (one of each type) in each 6-month cycle.

6.54 The evaluation considered that the modelling of a reduction in non-fatal stroke events with bempedoic acid treatment was not adequately supported by the results of the key trial which did not demonstrate a nominally significant difference in non-fatal stroke events between treatment arms.

6.55 The submission estimated a risk multiplier for patients with a history of MI based on an analysis of the Western Australia data linkage study (Nedkoff 2023). The estimate used in the submission (HR 1.31; 95% CI 1.07, 1.59) was based on a univariate analysis of the risk of a MACE event at 90 days in patients with a prior MI event. However, the risk associated with a prior MI did not remain statistically significant in multivariate analysis accounting for Indigenous status, age, sex, coronary revascularisation during index event, type of MI and cardiovascular comorbidities (HR 1.11; 95% CI 0.88, 1.39). Additionally, the risk estimate was only based on 90 days following the index event and is unlikely to reflect the long term risk in patients with a history of MI.

6.56 The submission estimated risk multipliers for patients with a history of stroke based on an analysis of linked data from Australian and New Zealand patients who were hospitalised for an initial stroke (65–74 years: 1.43; 75–85 years: 1.60; 80+ years: 1.54; Peng 2022). The estimates used in the submission were based on the hazard ratio for age as a predictor of recurrent stroke. The values used in the submission represent the risk relative to a reference population aged 18–54 years with a stroke rather than a population with no prior history of stroke. Therefore, these estimates are not appropriate to use as a prior stroke event risk multiplier in the model.

6.57 The submission assumed that coronary revascularisation procedures would have the same risk multiplier as MI (1.31). This assumption was not appropriate. Data from the Nedkoff (2023) publication noted that neither percutaneous coronary intervention nor coronary artery bypass grafting was associated with a statistically significant risk of MACE events within 90 days of the index event. The Sub-Committees agreed with the evaluation that the prior event risk multipliers applied to the economic model were highly uncertain.

6.58 The submission estimated a survival benefit for bempedoic acid on the basis that a proportion of MI and stroke events are fatal and therefore reducing the overall risk of these events would also reduce their associated mortality during the extrapolated period. The submission argued that this was reasonable as the PBAC previously considered that 'it is biologically plausible for the mortality benefit of lipid-lowering therapy to become evident over a longer time period, as reduction in LDL levels would first translate into plaque reduction or stabilisation, which then leads to reduced or delayed CV events, and subsequently fewer deaths' (para 4.7, evolocumab PSD, November 2019 PBAC meeting).

6.59 The submission estimated age-based risk multipliers for cardiovascular events based on the incidence of events reported in the AIHW Heart, stroke and vascular disease report 2025 (using data from 2023). The evaluation considered that the assumption that the estimated incidence of coronary heart disease hospitalisations from the AIHW data can be used as a proxy for unstable angina hospitalisations and coronary revascularisation procedures was not adequately supported. In particular, the AIHW report includes unstable angina in the estimates of acute coronary events which the submission has used to inform MI estimates. Additionally, a recent analysis of AIHW data (Kumar 2024) indicates that the use of coronary revascularisation procedures peaks in individuals aged 60–74 years and then declines thereafter which is not the same pattern observed for coronary heart disease hospitalisations. The evaluation noted that the AIHW estimates are based on the crude incidence of cardiovascular events and therefore risk multipliers derived from this data will overlap with risk estimates from the CLEAR OUTCOMES trial population (which included patients of varying ages: 41.3% <65 years, 43.6% 65-74 years, 15.1% >75 years) and will overlap with risk captured by the prior event risk multiplier.

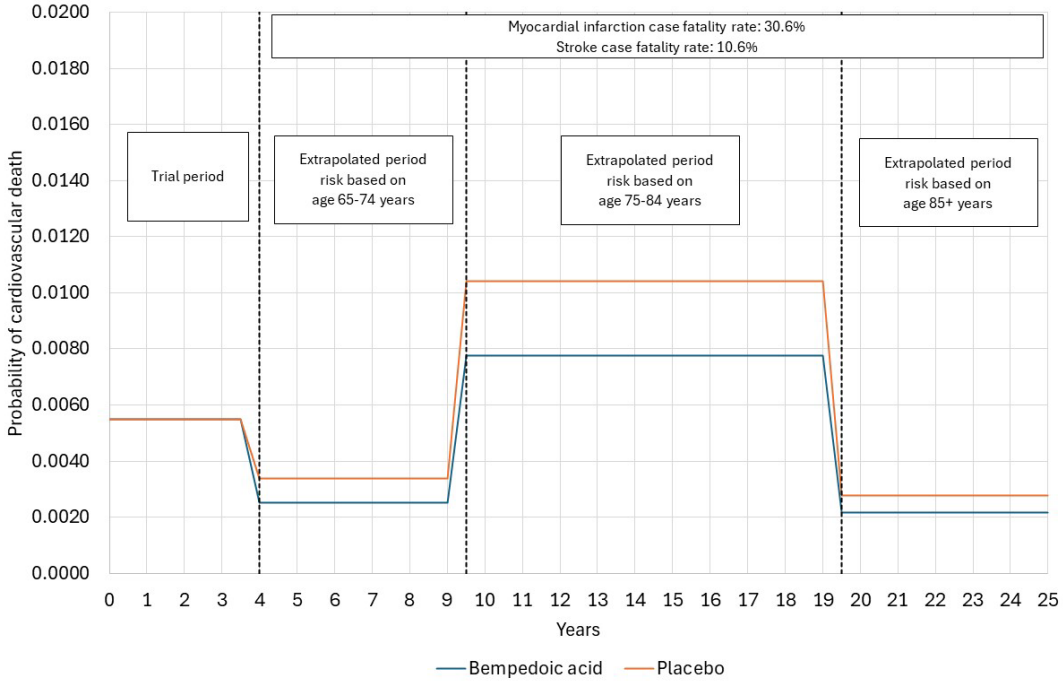
6.60 Case fatality rates (CFRs) were individually calculated for MI and stroke based on *post hoc* analyses of the CLEAR OUTCOMES trial data that reclassified adjudicated causes of cardiovascular death to either MI or stroke. The submission noted that a substantial number of patients had an undetermined cause of death which according to the CLEAR OUTCOMES trial protocol were classified as cardiovascular death. However, the submission argued that many of these cases may not have been modifiable by lipid lowering therapy. Therefore, the submission provided two approaches to handling these deaths as well as other unallocated deaths; either assuming these unallocated deaths do not occur or redistributing these unallocated deaths to MI and stroke (based on the ratio of mapped fatal MI and stroke events) and therefore assuming that these deaths are modifiable by lipid lowering therapy. The *post hoc* estimates of fatal MI and stroke events were then compared with the reported non-fatal estimates of these events in order to calculate individual CFRs. The evaluation considered that the submission did not adequately justify the mapping of specific adjudicated causes of death to either MI or stroke. In particular, it should be noted that higher allocation of events to MI versus stroke favours bempedoic acid as the model assumes a larger treatment effect for bempedoic acid on MI events.

6.61 A multinational study of MI CFRs in Australia, New Zealand, Canada and the United Kingdom was identified during the evaluation (Camacho 2023). This study reported CFRs for Australian patients of approximately 35% in 2002 which declined to approximately 23% in 2015 representing a 37.8% reduction in risk (average annual reduction of 3.4% per year). A similar pattern has also been reported in other Australian studies (Nedkoff 2022; abstract only). Overall, these studies suggest that the *post hoc* estimation of fatality rates from the CLEAR OUTCOMES trial (MI CFRs ranging from 28.2% to 56.1%) may be overestimated and not representative of Australian clinical practice.

6.62 The submission also assumed CFRs remain constant over time. The evaluation considered that this assumption was not adequately justified in the submission and appeared implausible. In general, CFRs would be expected to increase over time with patient age. Furthermore, the submission claimed it was appropriate to use CFRs for MI and stroke from the placebo arm for both treatment groups in the economic model as this avoided 'counter-intuitive' results in which bempedoic acid treatment was associated with higher CFRs than placebo.

6.63 CFRs were used in the economic model as scaling factors which were applied to age-adjusted estimates of non-fatal events in each treatment arm in order to derive a total event risk. Fatal events were then derived for each treatment arm by subtracting non-fatal events from the total event risk. The approach used in the submission resulted in transition probabilities that lacked face validity. The risk of cardiovascular death decreases in both treatment arms after the initial trial period as a substantial number of cardiovascular deaths (i.e. unallocated deaths) that occurred during the trial are assumed to not occur during the extrapolated period. The risk of death then substantially increases between 9.5 and 19 years and then sharply decreases after 19.5 years primarily due to the age-based risk multipliers applied to non-fatal cardiovascular events (which are used in the calculation of the total number of events that can be fatal) and the assumption that CFRs remain constant over time regardless of patient age (Figure 3).

Figure 3: Probability of cardiovascular death per cycle assuming the cardiovascular deaths that cannot be assigned to myocardial infarction or stroke do not occur (overall population)



Source: Constructed during the evaluation based on the 'Bempedoic acid economic model' provided with the submission.

6.64 The PSCR acknowledged that the case fatality mechanism implemented in the economic model resulted in implausible cardiovascular death transition probabilities.

To address this issue, the PSCR proposed age-varying CFRs based on AIHW data (Table 13, Web report 2025). The Sub-Committees noted that the values used in the PSCR could not be directly validated as the AIHW website updates Excel tables accompanying each web report. However, the values used in the PSCR can be compared to the current AIHW report (Web report 2026). There were notable differences in MI CFRs in patients aged 75–84 years (Web Report 2025: 17.4%; Web Report 2026: 28.7%) and patients aged 85+ years (PSCR Web Report 2025: 89.0%; Web Report 2026: 79.1%) across different AIHW datasets.

6.65 Overall, the Sub-Committees considered that given the validation issues noted above it may be more appropriate to switch estimates of age-varying CFRs and age-adjusted non-fatal cardiovascular event risk multipliers to estimates based on current AIHW Heart, stroke and vascular disease 2026 Web Report data. The Pre-PBAC Response provided a revised economic model in which these estimates were updated using current AIHW (2026) data.

Table 13:Trial-based and updated case fatality rates, by age and CV event

	Myocardial infarction		Stroke	
	Acute coronary event rate / coronary heart disease death rate per 100,000 persons	Case fatality (%)	Stroke event rate / stroke death rate per 100,000 persons	Case fatality (%)
AIHW Heart, stroke and vascular disease data (Web report 2025, PSCR)				
65-74 years	118/605	19.5%	39/354	11.0%
75-84 years	328/1,885*	17.4%	162/860	18.8%
85+ years	1,648/1,851	89.0%	783/2,104	37.2%
AIHW Heart, stroke and vascular disease data (Web report 2026)				
65-74 years	104/584	17.8%	39/353	11.0%
75-84 years	265/922	28.7%	145/820	17.7%
85+ years	1,290/1,630	79.1%	652/1,890	34.5%

Source: PSCR (p3), Web reports 2026 values from https://www.aihw.gov.au/reports/heart-stroke-vascular-diseases/hsvd-facts/data [Accessed 28 May 2026]

Note: All estimates were based on individual male and female calculations with a weighted overall result based on 51.8% male; 48.2% female, consistent with the bempedoic acid base case analysis

Abbreviations: AIHW, Australian Institute for Health and Welfare

*The acute coronary event rate for patients aged 75–84 years estimated from the Web Report 2025 (1,885) appears inconsistent with other reported values and appears to be a data imputation error (an estimate of 885 for this value would be more consistent with other AIHW datasets).

6.66 The submission estimated health state costs associated with chronic cardiovascular management using published Australian cost and cost effectiveness analyses (Ademi 2021, Abebe 2024, and Abebe 2025). The submission assumed that patients with a prior history of coronary revascularisation events would have the same health state costs as event-free patients. The submission also assumed that event-free costs are the same for the primary and secondary prevention populations. The evaluation considered that this assumption lacked face validity given the significant ongoing costs associated with cardiovascular disease captured in the model.

6.67 The model applied constant annual chronic health state costs for MI and stroke over the 25 year time horizon. This was inconsistent with data from Abebe 2025 and Abebe 2024 indicating that costs were highest in the first year following the event and decline

substantially over time. The Sub-Committees agreed with the evaluation that applying constant health state costs over time led to overestimated long-term costs associated with MI and stroke health states.

6.68 In the economic model, the costs associated with the event-free health state are added to the MI and stroke health state costs. However, the MI and stroke cost estimates from Abebe 2025 and Abebe 2024 included hospitalisation, pharmaceutical and other health care costs derived from linked data, including costs that are not directly attributable to the events. The Sub-Committees considered that adding the costs associated with the event-free health state resulted in double counting of health care costs and substantially overestimated the cost associated with MI and stroke health states.

6.69 The evaluation noted that a comparison of health state costs used in the model versus other published Australian studies suggested that estimated costs for MI in the model are approximately 4–10 times higher than other estimates while the costs of stroke are approximately 4 times higher than other estimates. The PSCR acknowledged that evidence from Abebe (2024) indicates that the estimate of $14,412 per patient per annum includes all health care costs and not just those costs attributable to the MI event. Therefore, the PSCR considered that the model could be updated to apply this cost per annum to the post-MI health state itself rather than adding it to the costs in the event free health state. The Pre-PBAC Response provided a revised economic model in which MI and stroke health state costs were not additive to event-free health state costs.

6.70 The Sub-Committees noted that Abebe (2024) reported the annual yearly cost of MI and noted that costs reduced over time (from $15,870 in year 1 to $8,482 in year 6). The Sub-Committees considered that all costs associated with events in the economic model should be high initially and reduce over time.

6.71 The PSCR provided a new estimate of the lifetime cost associated with stroke ($127,793) based on the Australian Stroke Foundation 2024 report on the Economic Impact of Stroke[4]. The PSCR claimed that using this estimate as an event cost (with no ongoing health state costs) would decrease the base case ICER in the overall population from $15,000 to < $25,000 to $15,000 to < $25,000 per QALY gained. However, the Sub-Committees considered that the inclusion of all stroke costs as a single upfront event cost is likely not appropriate as it does not represent the gradual accrual of costs over time nor adequately addresses the overlapping impact of multiple cardiovascular events. The PSCR also argued that this estimate of lifetime costs invalidates the older estimates of stroke health state costs. The Sub-Committees

[4] Source: Kim, J., Nivelle, E., Dalli, L.L., Zomer, E., Birhanu, M., Purvis, T., Olaiya, M.T., Talic, S., Kilkenny, M.F. and Cadilhac, D., 2024. Economic impact of stroke report 2024.https://strokefoundation.org.au/what-we-do/research/economic-impact-of-stroke-in-australia

noted that average chronic cost of stroke between 3 months and five years was $46,763 (Table 20, p58 of the Stroke Foundation 2024 report), which equates to an annual cost of $9,845 per year. This cost remains lower than the stroke health state costs used in the submission and is more consistent with the Year 6 costs from the Abebe 2024 publication. The Pre-PBAC Response argued that incorporating declining health state costs over time would require multiple overlapping tunnel health states. The Response provided a revised economic model which included a reduced annual post stroke and post MI cost. The annual post MI cost was reduced from $19,838.10 to $16,854.42 (Abebe 2025; overall adjusted total chronic cost per person, inflation of 1.1695x assumed) and the annual post stroke cost was reduced from $18,951.10 to $15,817.09 (Abebe 2024; overall adjusted total chronic costs per person, inflation of 1.1695x assumed). The annual event free health state cost was increased from $5,426.10 to $6,345.67 (inflation factor of 1.1695x assumed).

6.72 Overall, the Sub-Committees considered that the way in which costs were applied to the model was highly problematic and led to the costs associated with MI and stoke to be substantially overestimated. The Sub-Committees also noted that acute event costs were based on a range of different sources and should be based on AR-DRGs to isolate hospitalisation costs and ensure consistency. The Pre-PBAC Response argued that AR-DRG cost weights underestimate acute event costs because the healthcare costs associated with MIs, strokes and other cardiovascular events extend beyond hospital care. However, for illustrative purposes, the Pre-PBAC Response updated the economic model to apply acute event costs based on AR-DRG cost weights, inflated to 2026 prices.

6.73 Key drivers of the economic model are summarised in Table 14.

Table 14: Key drivers of the model

Description	Method/Value	Impact
Underlying cardiovascular risk	The submission argued that the modelled analyses based on the CLEAR OUTCOMES data are broadly generalisable to the PBS population and provide a reasonable basis for estimating the cost effectiveness of bempedoic acid on the PBS. The argument was not reasonable as the broader PBS population is likely to be at lower risk than the trial population given the differences in required LDL levels and use of background statin therapies. The modelling of a reduction in non-fatal stroke events with bempedoic acid treatment was not adequately supported by the results of the key trial which did not demonstrate a nominally significant difference in non-fatal stroke events between treatment arms.	High, favours bempedoic acid
Age-based risk multipliers for CV events	The assumption that the estimated incidence of coronary heart disease hospitalisations from the AIHW data can be used as a proxy for unstable angina hospitalisations and coronary revascularisation procedures was not adequately supported. The AIHW estimates are based on the crude incidence of cardiovascular events and therefore risk multipliers derived from this data will overlap with risk estimates from the CLEAR OUTCOMES trial population (which included patients of varying ages: 41.3% <65 years, 43.6% 65-74 years, 15.1% >75 years) and will overlap with risk captured by the prior event risk multiplier.	High, favours bempedoic acid

Description	Method/Value	Impact
Prior event risk multipliers	The risk multiplier for a history of MI (HR 1.31, 95% CI 1.07, 1.59; Nedkoff 2023) did not remain statistically significant in multivariate analysis and was only based on 90 days following the index event. It was unlikely to reflect the long-term risk in patients with a history of MI. This multiplier was also used for coronary revascularisation procedures. This assumption was not appropriate. The risk multipliers for patients with a history of stroke (65-74 years: 1.43; 75-85 years: 1.60; 80+ years: 1.54) are based on people aged 18-54 years with a stroke rather than a population with no prior history of stroke. This assumption was not appropriate.	High, direction variable
Case fatality rates	Case fatality rates were estimated based on post hoc analyses of the placebo arm of the CLEAR OUTCOMES trial that reclassified adjudicated causes of cardiovascular death to either MI or stroke. These estimates were applied as scaling factors to the age-adjusted non-fatal cardiovascular event risks for each arm to estimate the total risk of each event. The approach used in the submission resulted in transition probabilities that lacked face validity (i.e. the risk of cardiovascular death decreases in both arms after the trial period and patients aged 85 years and older have a decreased risk of cardiovascular death compared to younger patients). The PSCR acknowledged that the case fatality mechanism implemented in the economic model resulted in implausible cardiovascular death transition probabilities. These estimates were updated in the PSCR and Pre-PBAC Response (see paragraphs 6.64–6.65).	High, favours bempedoic acid
Health state costs	The assumption that event-free costs are the same for the primary and secondary prevention populations lacks face validity. The model applies constant annual chronic health state costs for MI and stroke over the 25 year time horizon. This is likely to overestimate the long-term costs associated with MI and stroke health states. In the economic model, the costs associated with the event-free health state are added to the MI and stroke health state costs. This resulted in double counting of health care costs and a substantially overestimated cost associated with MI and stroke health states. The Pre-PBAC Response provided a revised economic model with revision to costs (see paragraphs 6.66–6.72).	High, favours bempedoic acid

Abbreviations: AIHW, Australian Institute of Health and Welfare; CV, cardiovascular; HR, hazard ratio; LDL, low density lipoprotein cholesterol; MACE, major acute cardiovascular event; MI, myocardial infarction; PBAC Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; PSD, Public Summary Document

6.74 The results of the modelled economic evaluation of the submission are summarised in Table 15.

Table 15: Results of economic evaluation in statin-intolerant patients

Component	Bempedoic acid	Placebo	Increment
Primary prevention			
Costs	$[redacted]	$90,595	$[redacted]
QALYs	9.7982	9.7046	0.0936
		Incremental cost per QALY gained	**$[redacted]** [1]
Secondary prevention			
Costs	$[redacted]	$112,701	$[redacted]
QALYs	9.2163	9.1023	0.1140
		Incremental cost per QALY gained	**$[redacted]** [2]

Source: 'Bempedoic acid economic model' provided with the submission.
Abbreviations: QALY, quality adjusted life year
The redacted values correspond to the following ranges:
[1] *$35,000 to < $45,000*
[2] *$15,000 to < $25,000*

6.75 Based on the economic model of the submission, treatment with bempedoic acid was associated with an incremental cost per quality adjusted life year (QALY) gained of $35,000 to < $45,000 compared to placebo for the primary prevention of cardiovascular events in a statin-intolerant population.

6.76 For every 1,000 statin-intolerant patients without pre-existing cardiovascular disease who are treated with bempedoic acid versus placebo and followed up for 25 years, the economic evaluation of the submission (based on undiscounted values) estimated that there would be:

- 88 fewer non-fatal cardiovascular events (primarily MI, coronary revascularisation procedures and hospitalisations for unstable angina).
- An average increase in survival of 7 weeks per patient due to a reduced risk of fatal MI and stroke events.
- Improved quality of life associated with reduced occurrence of non-fatal cardiovascular events (average increase of 0.0487 quality-adjusted life years per patient after accounting for survival).
- Additional treatment costs ($9.4 million) which were partially offset by decreased acute cardiovascular events costs (-$1.4 million) and ongoing disease management costs for MI and stroke (-$4.9 million).

6.77 Based on the economic model of the submission, treatment with bempedoic acid was associated with an incremental cost per QALY gained of $15,000 to < $25,000 compared to placebo for the secondary prevention of cardiovascular events in a statin-intolerant population.

6.78 For every 1,000 statin-intolerant patients with pre-existing cardiovascular disease who are treated with bempedoic acid versus placebo and followed up for 25 years, the economic evaluation of the submission (based on undiscounted values) estimated that there would be:

- 171 fewer non-fatal cardiovascular events (primarily MI, coronary revascularisation procedures and hospitalisations for unstable angina).
- An average increase in survival of 9 weeks per patient due to a reduced risk of fatal MI and stroke events.
- Improved quality of life associated with reduced occurrence of non-fatal cardiovascular events (average increase of 0.0597 quality-adjusted life years per patient after accounting for survival).
- Additional treatment costs ($9.1 million) which were partially offset by decreased acute cardiovascular events costs (-$2.4 million) and ongoing disease management costs for MI and stroke (-$5.0 million).

6.79 Based on the economic model of the submission, treatment with bempedoic acid was associated with an incremental cost per QALY gained of $15,000 to < $25,000 compared to placebo for the overall population (30% primary, 70% secondary; based on the CLEAR OUTCOMES trial) of statin intolerant patients.

6.80 The Sub-Committees noted that the PBAC has not previously suggested an acceptable ICER for the specific target population nominated in the submission but has suggested acceptable ICERs of ≤$15,000–$25,000 per QALY gained for icosapent ethyl for established cardiovascular disease with elevated triglycerides (para 5.5, icosapent ethyl PSD, March 2024 PBAC meeting) as well as an ICER of ≤$25,000–$35,000 per QALY gained for evolocumab for established cardiovascular disease with elevated cholesterol levels and additional cardiovascular risk factors (para 7.11, evolocumab PSD, July 2022 PBAC meeting).

6.81 The results of key sensitivity analyses presented in the submission and conducted during the evaluation are summarised in Table 16. The economic model exhibited substantial uncertainty and overall, the evaluation considered the model was not reliable. The PSCR stated that the variability observed in the sensitivity analyses reflected extreme assumptions, rather than issues related to the model, and that results appear more consistent when more clinically plausible inputs are used.

Table 16: Results of key sensitivity analyses

Analysis	Primary prevention		Secondary prevention	
	ICER	Change from base case ICER	ICER	Change from base case ICER
Base case	$[redacted]1	-	$[redacted]2	-
Discount rate (base case: 5% for benefits and costs)				
3.5% discount rate	$[redacted]3	-[redacted]%	$[redacted]4	-[redacted]%
0% discount rate	$[redacted]2	-[redacted]%	$[redacted]4	-[redacted]%
Time horizon (base case: 25 years)				
30 years	$[redacted]3	-[redacted]%	$[redacted]2	-[redacted]%
20 years	$[redacted]5	+[redacted]%	$[redacted]2	+[redacted]%
Cardiovascular risk (base case: incidence of non-fatal events for each arm estimated from each subgroup of the CLEAR OUTCOMES trial; incidence of fatal cardiovascular events based on the placebo arm of the CLEAR outcomes trial for the initial 3.5 years and then extrapolated using data from the placebo arm to calculate case fatality rates for MI and stroke; risk multipliers for age and prior cardiovascular events)				
Decrease baseline risk of CVD events by 50%	$[redacted]6	+[redacted]%	$[redacted]7	+[redacted]%
Decrease baseline risk of CVD events by 30%	$[redacted]7	+[redacted]%	$[redacted]1	+[redacted]%
Decrease baseline risk of CVD events by 10%	$[redacted]1	+[redacted]%	$[redacted]2	+[redacted]%
Assume no bempedoic acid treatment effect on cardiovascular death	$[redacted]7	+[redacted]%	$[redacted]2	+[redacted]%
Estimate bempedoic acid treatment effects based on the reported hazard ratios for subgroup populations in CLEAR OUTCOMES	$[redacted]2	-[redacted]%	Southwest quadrant[a]	-
Estimate bempedoic acid treatment effects based on the reported upper CI of hazard ratios for subgroup populations in CLEAR OUTCOMES	$[redacted]8	+[redacted]%	Dominated	-
Estimate bempedoic acid treatment effects based on the reported lower CI of hazard ratios for subgroup populations in CLEAR OUTCOMES	$[redacted]4	-[redacted]%	Dominant	-
Include unallocated cardiovascular deaths in the CFR calculation	$[redacted]3	-[redacted]%	$[redacted]2	+[redacted]%
Estimate treatment-arm specific CFRs	$[redacted]3	-[redacted]%	$[redacted]2	+[redacted]%
Estimate treatment-arm specific CFRs and include unallocated cardiovascular deaths	$[redacted]3	-[redacted]%	Dominated	-

Analysis	Primary prevention		Secondary prevention	
	ICER	Change from base case ICER	ICER	Change from base case ICER
Base case	$[redacted][1]	-	$[redacted][2]	-
Use AIHW Heart, stroke and vascular disease 2026 Web Report to calculate age-adjusted non-fatal cardiovascular event risk multipliers plus age-varying CFRs (using the AIHW 2026 Web report)	$[redacted][5]	+[redacted]%	$[redacted][2]	+[redacted]%
Remove age-based risk multipliers	$[redacted][5]	+[redacted]%	$[redacted][2]	+[redacted]%
Remove prior event risk multipliers	$[redacted][1]	+[redacted]%	$[redacted][2]	+[redacted]%
Use the difference in risk between primary and secondary prevention subgroups in the placebo arm of the CLEAR OUTCOMES trial as a prior event risk multiplier (MI: 2.64, stroke: 1.41, coronary revascularisation: 2.93)	$[redacted][3]	-[redacted]%	$[redacted][4]	-[redacted]%
Circumstances of use (base case: all trial-based treatment discontinuations assumed to occur at 3.5 years with further discontinuations extrapolated from the bempedoic acid treatment arm of CLEAR OUTCOMES)				
Double treatment discontinuations in extrapolated period	$[redacted][1]	[redacted]%	$[redacted][2]	+[redacted]%
Health state costs (base case: event-free costs of $5,426 per year based on Ademi 2021; MI health state costs based on Abede 2025 ($14,412 per year) + event-free costs (total: $19,838 per year); stroke health state costs based on Abebe 2024 ($13,525 per year) + event-free costs (total $18,951 per year); coronary revascularisation health state costs assumed to be the same as event-free)				
Assume event-free health state costs are not additive to other health state costs ($5,426 per year removed from MI and stroke health states)	$[redacted][5]	+[redacted]%	$[redacted][3]	+[redacted]%
MI health state costs based on Year 1 estimates ($15,870) from Abebe 2025, not additive with event-free costs	$[redacted][5]	+[redacted]%	$[redacted][3]	+[redacted]%
MI health state costs based on Year 3 estimates ($11,677) from Abebe 2025, not additive with event-free costs	$[redacted][5]	+[redacted]%	$[redacted][3]	+[redacted]%
MI health state costs based on Year 6 estimates ($8,482) from Abebe 2025, not additive with event-free costs	$[redacted][7]	+[redacted]%	$[redacted][1]	+[redacted]%
Stroke health state costs based on Year 1 estimates ($14,309) from Abebe 2024, not additive with event-free costs	$[redacted][5]	+[redacted]%	$[redacted][3]	+[redacted]%
Stroke health state costs based on Year 3 estimates ($12,057) from Abebe 2024, not additive with event-free costs	$[redacted][5]	+[redacted]%	$[redacted][3]	+[redacted]%
Stroke health state costs based on Year 6 estimates ($9,776) from Abebe 2024, not additive with event-free costs	$[redacted][5]	+[redacted]%	$[redacted][3]	+[redacted]%

Source: 'Bempedoic acid economic model' provided with the submission.

Abbreviations: CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; ICER, incremental cost effectiveness ratio; MI, myocardial infarction.

[a] Bempedoic acid was less costly but less effective than placebo.

The redacted values correspond to the following ranges:

[1] *$35,000 to < $45,000*
[2] *$15,000 to < $25,000*
[3] *$25,000 to < $35,000*
[4] *$5,000 to < $15,000*
[5] *$45,000 to < $55,000*
[6] *$95,000 to < $115,000*
[7] *$55,000 to < $75,000*
[8] *$155,000 to < $255,000*

6.82 The results of the sensitivity analyses indicated that the model was most sensitive to discount rates, time horizon, baseline cardiovascular risk, age-based risk multipliers, prior event risk multipliers, bempedoic acid treatment effects, CFR calculations and MI health state costs.

6.83 The Sub-Committees noted that substantial uncertainty was associated with the economic model, with key uncertainties biasing results in favour of bempedoic acid. The Sub-Committees advised that the structure of the model was not aligned with the published literature[5,6] and considered that a microsimulation may have been more appropriate. However, the Sub-Committees considered that the economic model could be sufficiently reliable for decision-making with revisions addressing key uncertainties and poorly justified assumptions, as follows:

- Age-varying CFRs and age-adjusted non-fatal cardiovascular event risk multipliers should be based on the current AIHW Heart, stroke and vascular disease 2026 Web Report data;
- Higher discontinuation rates to reflect a non-trial setting. Ideally, this would be time dependent (higher initially);
- All acute event costs estimated using AR-DRG v11.0, Round 25 (2020-2021) cost weights;
- Post MI and post stroke health state costs should not be additive to event-free health state costs; and
- Health state costs should decline over time; or at the very least be reduced based on Abebe data.

6.84 However, the Sub-Committees noted that the revised base case remains optimistic, as it does not account for a reduced baseline risk, that would be expected in the requested broader PBS population compared to the trial population. The Pre-PBAC Response argued that it would be difficult to estimate how lowering the LDL threshold from 2.6 mmol/L to 1.8 mmol/L would affect baseline risk. The Response stated that this would depend on how often bempedoic acid would be used in patients with LDL levels between 1.8 and 2.6 mmol/L. The Response noted that uptake may be lower in this group than in patients with LDL >2.6 mmol/L, but patients most likely to be treated may have additional risk factors, such as diabetes, and therefore may be at higher risk than the average patient in this LDL range.

6.85 Due to the structural limitations of the economic model, discontinuation rates and health state costs could not vary over time. Therefore, alternative analyses were conducted as per the request of the Sub-Committees (Table 17, Table 18).

[5] Perera K, Kam N, Ademi Z, Liew D, Zomer E. Bempedoic acid for high-risk patients with CVD as adjunct lipid-lowering therapy: A cost-effectiveness analysis. J Clin Lipidol. 2020 Nov-Dec;14(6):772-783.

[6] Morton JI, Liew D, Watts GF, Zoungas S, Nicholls SJ, Dixon P, Ademi Z. Rethinking cardiovascular prevention: cost-effective cholesterol lowering for statin-intolerant patients in Australia and the UK. Eur J Prev Cardiol. 2025 Sep 22;32(13):1259-1270

Table 17: Additional analyses requested by Sub-Committees (primary prevention population)

Analysis	Incremental cost	Incremental QALY	ICER	Change from base case ICER
Submission base case	**$[redacted]**	**0.0936**	**$[redacted][1]**	**-**
Step 1: Use AIHW Heart, stroke and vascular disease 2026 Web Report to calculate age-adjusted non-fatal cardiovascular event risk multipliers	$[redacted]	0.0780	$[redacted][1]	+[redacted]%
Step 2: As for Step 1, plus age-varying CFRs (using the AIHW 2026 Web report)	$[redacted]	0.0622	$[redacted][2]	+[redacted]%
Step 3: As for Step 2, plus MI and stroke health state costs not additive to event-free health state costs	$[redacted]	0.0622	$[redacted][3]	+[redacted]%
Step 4: As for Step 3, plus MI ($8,482) and stroke ($9,776) health state costs based on Year 6 estimates from Abebe 2024/2025	$[redacted]	0.0622	$[redacted][4]	+[redacted]%
Step 5: As for Step 4, plus all acute event costs estimated using AR-DRG v11.0, Round 25 (2020-2021) cost weights[a,b]	$[redacted]	0.0622	$[redacted][4]	+[redacted]%
Step 6: As for Step 5, plus treatment discontinuations in the extrapolated period doubled	$[redacted]	0.0473	$[redacted][5]	+[redacted]%

Abbreviations: AIHW, Australian Institute for Health and Welfare; AR-DRG, Australian Refined Diagnosis Related Groups; ICER, incremental cost effectiveness ratio; MI, myocardial infarction; QALY, quality adjusted life year.

[a] Costs for MI were calculated based on F10A/B (Interventional Coronary Procedures, Admitted for AMI); F41A/B (Circulatory Disorders, Admitted for AMI with Invasive Cardiac Investigative Interventions); F60A/B (Circulatory Disorders, Admitted for AMI without Invasive Cardiac Investigative Interventions); weighted average cost $10,109 per event

[b] Costs for stroke were calculated based on AR-DRG items B70A/B/C/D (Stroke and Other Cerebrovascular Disorders); weighted average cost $10,600 per event

The redacted values correspond to the following ranges:

[1] *$35,000 to < $45,000*

[2] *$45,000 to < $55,000*

[3] *$55,000 to < $75,000*

[4] *$75,000 to < $95,000*

[5] *$95,000 to < $115,000*

6.86 Based on the revised base case (including all analyses requested by the Sub-Committees), treatment with bempedoic acid was associated with an incremental cost per QALY gained of $95,000 to < $115,000 compared to placebo in a primary prevention population of statin-intolerant patients with baseline LDL ≥2.6 mmol/L.

Table 18: Additional analyses requested by Sub-Committees (secondary prevention population)

Analysis	Incremental cost	Incremental QALY	ICER	Change from base case ICER
Submission base case	**$[redacted]**	**0.1140**	**$[redacted][1]**	**-**
Step 1: Use AIHW Heart, stroke and vascular disease 2026 Web Report to calculate age-adjusted non-fatal cardiovascular event risk multipliers	$[redacted]	0.0985	$[redacted][1]	+[redacted]%
Step 2: As for Step 1, plus age-varying CFRs (using the AIHW 2026 Web report)	$[redacted]	0.0861	$[redacted][1]	+[redacted]%
Step 3: As for Step 2, plus MI and stroke health state costs not additive to event-free health state costs	$[redacted]	0.0861	$[redacted][2]	+[redacted]%
Step 4: As for Step 3, plus MI ($8,482) and stroke ($9,776) health state costs based on Year 6 estimates from Abebe 2024/2025	$[redacted]	0.0861	$[redacted][3]	+[redacted]%
Step 5: As for Step 4, plus all acute event costs estimated using AR-DRG v11.0, Round 25 (2020-2021) cost weights[a,b]	$[redacted]	0.0861	$[redacted][4]	+[redacted]%
Step 6: As for Step 5, plus treatment discontinuations in the extrapolated period doubled	$[redacted]	0.0665	$[redacted][4]	+[redacted]%

Abbreviations: AIHW, Australian Institute for Health and Welfare; AR-DRG, Australian Refined Diagnosis Related Groups; ICER, incremental cost effectiveness ratio; MI, myocardial infarction; QALY, quality adjusted life year.

[a] Costs for MI were calculated based on F10A/B (Interventional Coronary Procedures, Admitted for AMI); F41A/B (Circulatory Disorders, Admitted for AMI with Invasive Cardiac Investigative Interventions); F60A/B (Circulatory Disorders, Admitted for AMI without Invasive Cardiac Investigative Interventions); weighted average cost $10,109 per event

[b] Costs for stroke were calculated based on AR-DRG items B70A/B/C/D (Stroke and Other Cerebrovascular Disorders); weighted average cost $10,600 per event

The redacted values correspond to the following ranges:

[1] *$15,000 to < $25,000*

[2] *$35,000 to < $45,000*

[3] *$45,000 to < $55,000*

[4] *$55,000 to < $75,000*

6.87 Based on the revised base case (including all analyses requested by the Sub-Committees), treatment with bempedoic acid was associated with an incremental cost per QALY gained of $55,000 to < $75,000 compared to placebo in a secondary prevention population of statin-intolerant patients with baseline LDL ≥2.6 mmol/L.

6.88 The Pre-PBAC Response provided an alternative base case, and included the following revisions:

- Age-varying CFRs and age-adjusted non-fatal cardiovascular event risk multipliers were revised and based on the current AIHW Heart, stroke and vascular disease 2026 Web Report data;
- Acute event costs were amended and estimated using AR-DRG v11.0, Round 25 (2020-2021) cost weights (described in the Pre-PBAC Response as 'illustrative only');
- Event-free health state costs were removed from the post MI and post stroke health states; and
- Health state costs were updated (MI = $16,854.42; stroke = $15,817.09; event free = $6,345.67).

However, the Pre-PBAC Response did not amend treatment discontinuation or account for a reduced baseline risk. The results of the revised economic model provided in the Pre-PBAC Response is shown in Table 19.

Table 19: Results of economic evaluation in statin-intolerant patients

Component	Bempedoic acid	Placebo	Increment
Primary prevention			
Costs	$[redacted]	$93,622	$[redacted]
QALYs	9.976	9.913	0.062
		Incremental cost per QALY gained	$[redacted][1]
Secondary prevention			
Costs	$[redacted]	$109,586	$[redacted]
QALYs	9.486	9.400	0.086
		Incremental cost per QALY gained	$[redacted][2]

Source: Pre-PBAC Response (p4) and accompanying economic model: 'Bempedoic_acid Economic model ESC response.xlsm'
Abbreviations: QALY, quality adjusted life year
The redacted values correspond to the following ranges:
[1] *$55,000 to < $75,000*
[2] *$25,000 to < $35,000*

6.89 The Pre-PBAC Response noted that based on the revised model, to achieve an ICER below $25,000 or $30,000 per QALY gained, the required DPMQ for bempedoic acid would be:

- Primary prevention population: $[redacted] and $[redacted], respectively.
- Secondary prevention population: $[redacted] and $[redacted], respectively.

The Pre-PBAC Response noted that the weighted DPMQ would be $[redacted] to achieve an ICER below $25,000 per QALY gained, and $[redacted] to achieve an ICER below $30,000 per QALY gained, based on a weighting of 26% for primary prevention and 74% for secondary prevention.

Drug cost/patient/year

6.90 The estimated drug costs for bempedoic acid per patient per year are summarised in Table 20.

Table 20: Drug cost per patient for bempedoic acid

	Trial	Economic model	Financial estimates
Cost per script (DPMQ)	-	Bempedoic acid single agent: $[redacted]	Bempedoic acid single agent: $[redacted] Bempedoic acid with ezetimibe FDC: $[redacted]
Treatment adherence	96.3%[a]	96.3%[a]	96.3%[a]
Cost per patient per year	-	$[redacted]	Bempedoic acid single agent: $[redacted] Bempedoic acid with ezetimibe FDC: $[redacted]
Treatment persistence	69.6% of patients remain on treatment at the end of the trial (median follow-up 3.4 years)	No discontinuation during the first 3.5 years however a compliance adjustment was applied to drug costs to account for imperfect persistence during this period. At 4 years, 30.4% (1- 69.6%) of patients were assumed to discontinue therapy based on the CLEAR OUTCOMES trial. From 4.5 years onwards, discontinuation is modelled as a constant per-cycle (6 months) probability (5.0%) based on the reported treatment discontinuation rate in the CLEAR OUTCOMES trial.	Not included

Source: Constructed during the evaluation using the Section 3 economic model Excel workbook and Table 4.1.13, p249 of the submission
Abbreviations: DPMQ, dispensed price maximum quantity; FDC, fixed dose combination
[a] Based on the proportion of patients achieving at least 80% treatment adherence with single agent bempedoic acid in the CLEAR OUTCOMES trial (i.e. the proportion of tablets taken)

6.91 The key differences between the sections of the submission were the inclusion/exclusion of bempedoic acid with ezetimibe FDC and the handling of treatment persistence.

Estimated PBS usage & financial implications

6.92 This submission was jointly considered by DUSC and ESC.

6.93 The submission used a mixed market share and epidemiological approach to estimate the utilisation and financial impact of listing bempedoic acid on the PBS/RPBS for a mixed population of patients with hypercholesterolaemia. The Sub-Committees considered that combining primary and secondary prevention patient populations into a single pool of patients and mixing statin-intolerant patients with those on maximally tolerated statin therapy was not appropriate, as these patient groups have distinct LDL profiles and different treatment behaviours.

6.94 The Pre-PBAC Response provided revised financial estimates that separated the primary and secondary prevention populations, based on the assumption that 69% of ezetimibe patients had prior ASCVD, consistent with the July 2022 submission for evolocumab.

6.95 The key inputs used to derive the financial implications are presented in Table 21.

Table 21: Key inputs for financial estimates

Parameter	Value	Source	Comment
Population: Mixed hypercholesterolaemia population who are using ezetimibe and who are statin-intolerant or who are inadequately controlled despite using a maximally tolerated dose of statins for primary and secondary prevention of cardiovascular disease			
Patients treated with ezetimibe (includes single agent and FDC)	Yr 1: 752,993 Yr 2: 832,646 Yr 3: 920,724 Yr 4: 1,018,119 Yr 5: 1,125,817 Yr 6: 1,244,908	Based on data from the 100% PBS sample on the number of unique patients using ezetimibe items (single agent and FDC) between 2019/2020 and 2023/2024 financial years. The submission claimed that it was appropriate to limit utilisation data prior to ezetimibe switching to an unrestricted benefit (30-day dispensing) or restricted benefit (60-day dispensing) in November 2024 on the basis that the older Streamlined Authority restriction required ezetimibe patients to be statin intolerant or using a maximally tolerated statin dose. The submission extrapolated patient estimates to subsequent years using an exponential function on the basis that this function had the best fit to the available data.	The submission did not adequately justify grouping all ezetimibe PBS items together. During the evaluation, an analysis of ezetimibe script data indicated that ezetimibe single agent (best fitting: exponential) and ezetimibe FDCs (best fitting: logarithmic) appear to be following different growth trajectories. This difference in growth trajectories may be partially due to the introduction of 60-day dispensing which appears to have had substantial uptake particularly for patients using ezetimibe single agent. The exclusion of utilisation data after ezetimibe switched to unrestricted/restricted benefit was inadequately justified given that this approach removes the most recent data on utilisation. However, this exclusion had a minimal impact on the budget impact estimates. The Sub-Committees considered that these data were a conservative choice as it aligns with the add-on indication, relies on real treated patients rather than hypothetical epidemiological estimates, and is likely to underestimate rather than overestimate the eligible population and associated costs, as there would be a proportion of people eligible but not using ezetimibe. The Sub-Committees agreed with the commentary regarding the differing growth trajectories for ezetimibe single agent compared with ezetimibe FDCs. The Sub-Committees considered that the exponential extrapolation may overestimate utilisation and considered a linear extrapolation may be more appropriate. The Pre-PBAC Response provided revised financial estimates, which applied a linear extrapolation for growth in ezetimibe patients.
Proportion of patients who are statin intolerant or using a maximally tolerated statin dose	64.2%	Based on the 2017 post-market review of ezetimibe use under the PBS. The analysis presented in the report was based on utilisation data from the 100% PBS sample on the number of unique patients using ezetimibe between April 2012 and March 2016. The estimate used in the submission was based on 18.4% of patients not meeting statin eligibility requirements and the assumption that half of the patients with unknown eligibility status (34.8%/2 = 17.4%) would	The Sub-Committees agreed with the evaluation that utilisation data informing these estimates was relatively old and may not reflect current clinical practice. The Sub-Committees noted that the PBS restriction for ezetimibe during 2020–2024 already required patients to either be statin-intolerant or on a maximally tolerated statin dose. Therefore, the Sub-Committees considered this adjustment was not required and would potentially underestimate the eligible population. The Pre-PBAC Response argued that not all ezetimibe prescriptions are consistent with the PBS restriction, and that DUSC had previously

Parameter	Value	Source	Comment
		also not meet the statin eligibility requirements. This assumption was consistent with previous PBAC considerations of ezetimibe (para 4.1, ezetimibe PBAC minutes, July 2017 PBAC meeting).	considered that 35.8% of ezetimibe use was outside the PBS listing.
Proportion of patients with LDL >1.8 mmol/L despite treatment with ezetimibe	37.2%	Based on the CODE RED report (Carrington 2020) using general practice data from the MedicineInsight database for 107,664 Australian adults with an index cardiovascular event between 2010 and 2019 with ≥1 recorded LDL value within 12 months of receiving a lipid-lowering therapy. The estimate used in the submission was based on the weighted average proportion of patients with LDL ≥1.8 mmol/L using: ezetimibe monotherapy (34% of overall ezetimibe use; 55% of monotherapy patients not achieving LDL target) and ezetimibe in combination with statin therapy (66% of overall ezetimibe use; 18% of combination patients not achieving LDL target).	The evaluation noted that estimates were based on a secondary prevention population, and it is unclear whether these estimates can be generalised to a primary prevention population. There were substantial differences in the proportion of patients failing to achieve lipid targets with ezetimibe monotherapy and ezetimibe combination therapy and it is unclear whether these values should be combined in an overall estimate. Additionally, the proportion of patients failing to achieve lipid targets is likely to vary further once the background intensity of statin therapy is considered (low, medium or high intensity). The Sub-Committees considered 37.2% was an underestimate as CODE RED reflects only a secondary prevention population. The Sub-Committees considered that it was not appropriate to apply this value to the primary prevention population given that the proportion of patients not achieving LDL targets would differ. The Sub-Committees considered that based on multiple sources that include primary and secondary prevention approximately 75% (primary) and 65% (secondary) of patients on ezetimibe would have LDL >1.8 mmol/L (Marquina, DA VINCI, SANTORINI, GOULD, EUROASPIRE). The Pre-PBAC Response provided revised financial estimates which increased the percentage of patients with LDL >1.8 mmol/L despite ezetimibe in both groups from 37.2% to 75% and 65% in the primary and secondary prevention populations, respectively.
Bempedoic acid uptake rates	Yr 1: [redacted]% Yr 2: [redacted]% Yr 3: [redacted]% Yr 4: [redacted]% Yr 5: [redacted]% Yr 6: [redacted]%	Assumption on the basis that statin intolerant patients and patients using maximally tolerated statin doses have no viable treatment alternatives to manage cardiovascular risk caused by their high cholesterol levels.	The submission did not adequately justify the assumption that both populations (statin intolerant and maximally tolerated statin) would have the same uptake rates given that cholesterol levels are likely to be better managed in patients with at least some exposure to statin therapy. The Sub-Committees agreed with the evaluation that it was not appropriate to assume the same uptake rates for statin-intolerant and maximally tolerated statin patient populations. Statin-intolerant patients typically have higher LDL levels, fewer treatment options and a greater unmet need. Whereas patients on maximally tolerated statin therapy generally have better LDL control and less clinical urgency.

<table>
<tr><th>Parameter</th><th>Value</th><th>Source</th><th>Comment</th></tr>
<tr><td></td><td></td><td></td><td>The Sub-Committees also considered there would be a lower uptake in primary prevention and higher uptake in secondary prevention.
The Pre-PBAC Response provided revised financial estimates in which the uptake in the maximally tolerated statin population was reduced by [redacted]% relative to the statin intolerant population, and the uptake in the secondary prevention population was [redacted]% greater than that in the primary population.
<table>
<tr><th></th><th>Year 1</th><th>Year 2</th><th>Year 3</th><th>Year 4</th><th>Year 5</th><th>Year 6</th></tr>
<tr><td>Primary, Statin intolerant</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td></tr>
<tr><td>Primary, Max tolerated statin</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td></tr>
<tr><td>Secondary, Statin intolerant</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td></tr>
<tr><td>Secondary, Max tolerated statin</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td></tr>
</table></td></tr>
<tr><td colspan="4">Proposed Medicine: Bempedoic acid and bempedoic acid with ezetimibe fixed dose combination</td></tr>
<tr><td>Scripts per patient per year</td><td>11.72</td><td>Based on reported adherence to bempedoic acid from the CLEAR OUTCOMES trial (96.3%) applied to number of scripts required for perfect coverage (12.18 script per year)</td><td>The evaluation noted that adherence estimates reported in a tightly regulated clinical trial setting are unlikely to be representative of clinical practice.

The evaluation noted that the estimate was also inconsistent with PBS data on ezetimibe utilisation which suggests an average of approximately 9.5 scripts per year (although this estimate may vary between different ezetimibe items).

The Sub-Committees noted that the estimated scripts per patient per year did not account for patients discontinuing therapy over time which was inconsistent with the economic model. The Sub-Committees considered that ideally, discontinuation (and adherence) would be aligned across the economic and financial models.

The Sub-Committees considered the number of scripts per patient per year was likely overestimated. The average is likely to be approximately 9.5 scripts per patient per year when assuming an adherence rate of 75–78%.

The Sub-Committees also noted that across PBS and primary-care studies (Ademi et al., 2023; Talic et al., 2022; Talic et al., 2023; Orman et al., 2024), 12-month adherence typically ranges from 50–70%, with substantial early discontinuation. Similar adherence levels are observed for other chronic oral cardiometabolic medicines. The Pre-PBAC Response provided revised financial estimates which assumed 9.5 scripts per patient per year.</td></tr>
</table>

Parameter	Value	Source	Comment
Proportion of use of single agent bempedoic acid	48.8%	Based on the CODE RED report (Carrington 2020). Based on the number of patients failing to achieve lipid targets with ezetimibe monotherapy (2,010) or ezetimibe combination therapy (1,918) / total number of ezetimibe patients failing to achieve lipid targets (3,928). The submission assumed that patients using ezetimibe monotherapy would switch to bempedoic acid with ezetimibe FDC while patients using ezetimibe in combination with a statin would use single agent bempedoic acid.	See issues related to the proportion of patients failing to achieve lipid targets above. The Sub-Committees considered these percentages may be reasonable, given the large proportion of patients in the proposed population already being treated with ezetimibe. As such, many patients would either continue ezetimibe plus bempedoic acid or switch to the fixed-dose combination. The Sub-Committees noted that real-world practice in Australia and internationally is characterised by stepwise escalation of lipid-lowering therapy. This approach generally favours statin monotherapy followed by the addition of separate agents, rather than the use of fixed-dose combinations. The Sub-Committees noted no real-world evidence was identified describing the proportion of patients receiving bempedoic acid as monotherapy versus fixed-dose combination with ezetimibe.
Proportion of use of bempedoic acid FDC	51.2%		
DPMQ	Bempedoic acid: $[redacted] Bempedoic acid FDC: $[redacted]	DPMQs estimated based on Administration, Handling and Infrastructure Fee, dispensing fees and wholesaler mark-up as of 1 January 2026.	-
Patient copayment	$14.05 per script	Based on the weighted average distribution of patients across beneficiary categories for evolocumab PBS items in 2025.	It was unclear whether this distribution would be representative of bempedoic acid given that patients eligible for evolocumab treatment under the PBS only represent a small subset of the requested PBS population for bempedoic acid. The Sub-Committees agreed with the evaluation.
Affected Medicine: Ezetimibe single agent (in statin intolerant patients)			
Scripts per patient per year	11.72	Assumption. Same as bempedoic acid.	The Sub-Committees agreed with the evaluation that this assumption was not appropriate given that PBS data on ezetimibe utilisation suggests an average of approximately 9.5 scripts per year. The Pre-PBAC Response did not provide financial estimates for affected medicines.
DPMQ	Ezetimibe: $18.47	Based on the current DPMQ for single agent ezetimibe	This was reasonable
Patient copayment	$14.05 per script	Based on the weighted average distribution of patients across beneficiary categories for evolocumab PBS items in 2025.	The Sub-Committees agreed with the evaluation that this was not appropriate and the average patient copayments for ezetimibe should be based on ezetimibe utilisation data.

Source: Table 4.1.13, p249 of the submission
Abbreviations: FDC, fixed dose combination; LDL, low density lipoprotein cholesterol; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme

6.96 The estimated utilisation and net financial implications of listing bempedoic acid on the PBS/RPBS for hypercholesterolaemia is summarised in Table 22.

Table 22: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total patients treated with bempedoic acid	[redacted][1]	[redacted][2]	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]
Scripts for single agent	[redacted][4]	[redacted][5]	[redacted][6]	[redacted][7]	[redacted][8]	[redacted][9]
Scripts FDC	[redacted][4]	[redacted][5]	[redacted][6]	[redacted][10]	[redacted][11]	[redacted][9]
DPMQ less co-pay	$[redacted][17]	$[redacted][18]	$[redacted][19]	$[redacted][20]	$[redacted][20]	$[redacted][20]
Cost offsets for substituted single agent ezetimibe, DPMQ less copay	-$[redacted][21]	-$[redacted][21]	-$[redacted][21]	-$[redacted][21]	-$[redacted][21]	-$[redacted][21]
Net PBS/RPBS cost	$[redacted][17]	$[redacted][18]	$[redacted][19]	$[redacted][22]	$[redacted][20]	$[redacted][20]
Pre-PBAC Response						
Primary, Statin intolerant	[redacted][12]	[redacted][13]	[redacted][13]	[redacted][14]	[redacted][1]	[redacted][1]
Primary, Max tol statin	[redacted][12]	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][14]	[redacted][14]
Secondary, Statin intolerant	[redacted][14]	[redacted][15]	[redacted][2]	[redacted][16]	[redacted][23]	[redacted][1]
Secondary, Max tol statin	[redacted][13]	[redacted][1]	[redacted][15]	[redacted][2]	[redacted][16]	[redacted][23]
Total Patients	[redacted][2]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][24]	[redacted][24]
Scripts						
Primary, Statin intolerant, FDC	[redacted][23]	[redacted][4]	[redacted][4]	[redacted][24]	[redacted][24]	[redacted][5]
Primary, Max tolerated statin, single agent	[redacted][16]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][24]	[redacted][24]
Secondary, Statin intolerant, FDC	[redacted][24]	[redacted][6]	[redacted][7]	[redacted][10]	[redacted][11]	[redacted][9]
Secondary, Max tolerated statin, single agent	[redacted][4]	[redacted][5]	[redacted][5]	[redacted][7]	[redacted][10]	[redacted][8]
Total Scripts	[redacted][7]	[redacted][25]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][26]
DPMQ less co-pay[a]	$[redacted][18]	$[redacted][27]	$[redacted][20]	$[redacted][20]	$[redacted][20]	$[redacted][28]

Source: Table 4.1.5, p244, Table 4.1.6, p245; Table 4.1.7, p246; Table 4.1.8, p246; Table 4.1.10, p247; Table 4.2.1, p250; Table 4.2.2, p250; Table 4.4.1, p251 of the submission. The Pre-PBAC Response and accompanying excel spreadsheet: 'Bempedoic acid Section 4 workbook ESC response.xlsx'

Abbreviations: DPMQ, dispensed price for maximum quantity; FDC, fixed dose combination; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme

[a] The Pre-PBAC Response did not provide the financial estimates for affected medicines.

The redacted values correspond to the following ranges:

[1] *30,000 to < 40,000*
[2] *50,000 to < 60,000*
[3] *70,000 to < 80,000*
[4] *100,000 to < 200,000*
[5] *300,000 to < 400,000*
[6] *400,000 to < 500,000*
[7] *500,000 to < 600,000*
[8] *700,000 to < 800,000*
[9] *1,000,000 to < 2,000,000*
[10] *600,000 to < 700,000*
[11] *800,000 to < 900,000*
[12] *5,000 to < 10,000*
[13] *10,000 to < 20,000*
[14] *20,000 to < 30,000*
[15] *40,000 to < 50,000*
[16] *60,000 to < 70,000*
[17] *$30 million to < $40 million*
[18] *$50 million to < $60 million*
[19] *$70 million to < $80 million*
[20] *$100 million to < $200 million*
[21] *net cost saving*

[22] *$90 million to < $100 million*
[23] *80,000 to < 90,000*
[24] *200,000 to < 300,000*
[25] *90,000 to < 100,000*
[26] *2,000,000 to < 3,000,000*
[27] *$90 million to < $100 million*
[28] *$200 million to < $300 million*

6.97 The estimated net cost to the PBS/RPBS for bempedoic acid and bempedoic acid with ezetimibe fixed dose combination in a mixed population with hypercholesterolaemia was estimated by the submission to be $30 million to < $40 million in Year 1, increasing to $100 million to < $200 million in Year 6, with a cumulative net cost of $900 million to < $1 billion over the first 6 years of listing. The Pre-PBAC Response did not provide the financial estimates for affected medicines (ezetimibe). The Pre-PBAC Response estimated that the cost to the PBS/RPBS (DPMQ less co-pay) would be $50 million to < $60 million in Year 1, increasing to $200 million to < $300 million in Year 6, with a cumulate cost of $900 million to < $1 billion over the first 6 years of listing.

6.98 The proportion of patients meeting the statin eligibility requirements was based on the 2017 post-market review of ezetimibe which assessed the proportion of use outside the PBS restriction. However, the data are relatively old and may not reflect current clinical practice. Additionally, the sponsor acknowledged that bempedoic acid may also be used outside of the requested restriction in a similar manner to ezetimibe and therefore using this proportion will underestimate utilisation of bempedoic acid. However, the submission argued that this proportion is important to quantify for the purposes of any future risk sharing arrangement. The Sub-Committees noted that the PBS restriction for ezetimibe during 2020–2024 already required patients to either be statin-intolerant or on a maximally tolerated statin dose. Therefore, the Sub-Committees considered this adjustment may not be required and would likely underestimate the eligible population. The Pre-PBAC Response argued that not all ezetimibe prescriptions are consistent with the PBS restriction, and that DUSC had previously considered that 35.8% of ezetimibe use was outside the PBS listing.

6.99 The evaluation noted that the submission assumed a relatively high uptake of bempedoic acid on the basis that patients have no viable treatment alternatives to manage cardiovascular risk caused by their high cholesterol levels. However, it is unclear whether these uptake rates would be achieved in clinical practice for both the statin-intolerant and maximally tolerated statin populations. The Sub-Committees agreed with the evaluation that it was not appropriate to assume the same uptake rates for statin-intolerant and maximally tolerated statin patient populations. Statin-intolerant patients typically have higher LDL levels, fewer treatment options and a greater unmet need. Whereas patients on maximally tolerated statin therapy generally have better LDL control and less clinical urgency. The Sub-Committees also considered there would be a lower uptake in primary prevention and higher uptake in secondary prevention. The Pre-PBAC Response provided revised financial estimates in which the uptake in the maximally tolerated statin population was reduced by [redacted]%

relative to the statin intolerant population, and the uptake in the secondary prevention population was [redacted]% greater than that in the primary population.

6.100 The estimated number of bempedoic acid scripts per patient per year (11.72) was derived from trial-based estimates of adherence which are unlikely to be reflective of clinical practice. Additionally, the estimates do not include the impact of imperfect persistence which is likely to be substantial in the target patient population. The Sub-Committees noted that the estimated scripts per patient per year did not account for patients discontinuing therapy over time which was inconsistent with the economic model. The Sub-Committees considered the average is likely to be approximately 9.5 scripts per patient per year when assuming an adherence rate of 75–78%. The Sub-Committees considered that ideally, discontinuation (and adherence) would be aligned across the economic and financial models. The Pre-PBAC Response provided revised financial estimates which assumed 9.5 scripts per patient per year.

6.101 Key sensitivity analyses performed on the financial estimates are presented in Table 23. The Sub-Committees noted the sensitivity analyses conducted during the evaluation and considered that the inputs most important to consider were the assumed extrapolation for ezetimibe patients (base case: exponential), the percentage of ezetimibe patients who met statin eligibility (base case: 64.2%), percentage of patients with LDL >1.8 mmol/L (base case: 37.2%), uptake rates, and the scripts per patient per year.

Table 23: Key sensitivity analyses of the financial estimates

Analysis	Cumulative net PBS/RPBS cost over 6 years	% change from base case
Base case (patient numbers estimated using an exponential function prior to the ezetimibe shift to restricted benefit, 64.2%% met statin eligibility requirements, 37.2%% have LDL >1.8 mmol/L, uptake increases from [redacted]% in Year 1 to [redacted]% in Year 6; 11.72 bempedoic acid scripts per patient per year)	**$[redacted][1]**	**-**
Extrapolate ezetimibe patient numbers using a linear function and utilisation data prior to the shift to restricted benefit	$[redacted][2]	-20%
Extrapolate ezetimibe patient numbers using a logarithmic function and utilisation data prior to the shift to restricted benefit	$[redacted][3]	-40%
Assume all patients using ezetimibe met statin eligibility requirements (100%)	$[redacted][4]	+56%
Increase the proportion of ezetimibe patients who met statin eligibility requirements by 10% (74.2%)	$[redacted][5]	+16%
Decrease the proportion of ezetimibe patients who met statin eligibility requirements by 10% (54.2%)	$[redacted][2]	-16%
Increase the proportion of patients with LDL >1.8 mmol/L despite treatment with ezetimibe by 10% (47.2%)	$[redacted][6]	+27%
Decrease the proportion of patients with LDL >1.8 mmol/L despite treatment with ezetimibe by 10% (27.2%)	$[redacted][2]	-27%
Estimate the proportion of patients with LDL >1.8 mmol/L based on data from the CODE RED report on ezetimibe monotherapy (55%)	$[redacted][4]	+48%
Estimate the proportion of patients with LDL >1.8 mmol/L based on data from the CODE RED report on ezetimibe with statin combination therapy (18%)	$[redacted][7]	-52%
Increase uptake rates by 20% in each year	$[redacted][6]	+38%
Decrease uptake rates by 10% in each year	$[redacted][2]	-24%
Decrease estimated scripts per patient per year to 10 for all therapies	$[redacted][2]	-15%

Analysis	Cumulative net PBS/RPBS cost over 6 years	% change from base case
Base case (patient numbers estimated using an exponential function prior to the ezetimibe shift to restricted benefit, 64.2%% met statin eligibility requirements, 37.2%% have LDL >1.8 mmol/L, uptake increases from [redacted]% in Year 1 to [redacted]% in Year 6; 11.72 bempedoic acid scripts per patient per year)	$[redacted][1]	-
Decrease estimated scripts per patient per year to 9 for all therapies	$[redacted][2]	-23%

Source: Table 4.6.1, p253 of the submission and conducted during the evaluation.
Abbreviations: LDL, low density lipoprotein cholesterol; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme
The redacted values correspond to the following ranges:
[1] *$500 million to < $600 million*
[2] *$400 million to < $500 million*
[3] *$300 million to < $400 million*
[4] *$800 million to < $900 million*
[5] *$600 million to < $700 million*
[6] *$700 million to < $800 million*
[7] *$200 million to < $300 million*

6.102 The results of the sensitivity analyses indicated that the budget impact estimate was sensitive to the extrapolation of patient estimates, the proportion of patients meeting statin eligibility requirements, the proportion of patients with elevated LDL levels, the estimated uptake rate and treatment compliance.

6.103 The Sub-Committees considered that the utilisation estimates were likely underestimated. The Sub-Committees suggested the following:

- Given that primary and secondary prevention patient groups have distinct LDL profiles and different treatment behaviours, these populations should be separated;
- Remove the percentage of patients who are statin intolerant or using a maximally tolerated statin dose, provided that it was already a requirement for the PBS restriction for ezetimibe during 2020–2024;
- Increasing the percentage of patients with LDL >1.8 mmol/L despite treatment with ezetimibe in both groups from 37.2% to approximately 75% (primary prevention) and 65% (secondary prevention); and
- Change the scripts per patient per year to 9.5 for bempedoic acid and ezetimibe, given that PBS data on ezetimibe utilisation suggests an average of approximately 9.5 scripts per year.

6.104 The Sub-Committees also considered the following should be considered:

- Aligning the treatment discontinuation across the economic and financial models;
- Modelling a lower uptake in primary prevention and higher uptake in secondary prevention;
- Linear extrapolation for growth in ezetimibe patients;
- Exploring recent market share scenarios for single agents versus fixed-dose combinations;

- Potential for use outside the current restriction.

6.105 As noted above, the Pre-PBAC Response provided revised financial estimates aligned with edits suggested by the Sub-Committees. However, the revised estimates did not remove the percentage of patients who are statin intolerant or using a maximally tolerated statin dose. The Pre-PBAC Response argued that not all ezetimibe prescriptions are consistent with the PBS restriction, and that DUSC had previously considered that 35.8% of ezetimibe use was outside the PBS listing.

6.106 The Pre-PBAC Response stated that further extrapolation of market-share scenarios for ezetimibe monotherapy versus fixed-dose combination therapy was unlikely to materially affect the net financial estimates. This was because the budget impact analysis was driven mainly by the incremental cost of bempedoic acid, with ezetimibe effectively cost-minimised as background therapy. Any variation in ezetimibe use as monotherapy or fixed-dose combination therapy was therefore expected to have only a marginal effect on overall costs, largely limited to small differences in patient co-payments.

Financial Management – Risk Sharing Arrangements

6.107 The Pre-PBAC Response recognised the substantial PBS/RPBS expenditure associated with the proposed listing of bempedoic acid and noted that some form of risk-sharing arrangement may be required. However, it considered that a [redacted]% rebate above the cap would be impractical because the FDC includes ezetimibe, which is supplied without a cap as monotherapy, and some above-cap use may be cost-effective if the eligible population was underestimated. The Response also noted that, given the low unit cost of bempedoic acid, distribution costs comprise around 30% of the DPMQ, making a [redacted]% rebate financially unviable.

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

7 PBAC Outcome

7.1 The PBAC did not recommend bempedoic acid and bempedoic acid with ezetimibe for the treatment of adult patients with hypercholesterolaemia (heterozygous familial (HeFH) and non-familial) at high risk of a first cardiovascular event or with established symptomatic atherosclerotic cardiovascular disease (ASCVD) who have statin intolerance or are on maximally tolerated statin therapy, and despite treatment with ezetimibe, continue to have low-density lipoprotein cholesterol (LDL) levels greater than 1.8 mmol/L. The PBAC accepted there was a clinical need for additional oral lipid lowering therapies for patients with statin intolerance or those with inadequate lipid control on statins or ezetimibe that are not eligible for PCSK9 inhibitors. The PBAC noted that the clinical trial evidence suggested bempedoic acid reduced major adverse cardiovascular events (MACE) and LDL cholesterol compared with placebo. However, the PBAC considered that the applicability of the main trial to the proposed PBS population was uncertain, as the outcomes from the higher-risk trial population overestimated the reduction in MACE to a broader, lower-risk proposed PBS

population. The PBAC considered the applicability of the trial data to the economic model was also an issue. The PBAC considered the economic model was subject to additional uncertainty that was substantial and required further revision, particularly in relation to the modelling of costs over time. The PBAC considered that a price reduction was likely required to achieve a cost-effective listing, together with a risk sharing arrangement.

7.2 The PBAC considered that the primary reason for this outcome was the economic evaluation.

7.3 The PBAC noted and welcomed the comments from health professionals and organisations supporting the PBS listing of bempedoic acid. The input emphasised that bempedoic acid addressed an important treatment gap, particularly for statin intolerant patients and other patients who require further LDL lowering but are not eligible for injectable therapies under the current PBS criteria. The input noted the benefits of bempedoic acid included its oral administration, which may be consistent with patient preferences, a potential cost advantage relative to PCSK9 inhibitors, favourable tolerability, and evidence from CLEAR OUTCOMES demonstrating fewer cardiovascular events with bempedoic acid compared with placebo in statin-intolerant patients. The PBAC acknowledged that there remains a clinical need for additional treatment options, particularly for patients who are not adequately managed with statins or ezetimibe but are not eligible for PCSK9 inhibitors.

7.4 The PBAC noted that the proposed clinical place for bempedoic acid was for the treatment of patients with hypercholesterolaemia (HeFH and non-familial) with LDL levels >1.8 mmol/L despite treatment with ezetimibe, who are either at high risk for a CV event (high risk primary prevention) or have established symptomatic ASCVD (secondary prevention), with a history of statin intolerance or who are receiving maximally tolerated statin therapy. The PBAC considered that this was likely reasonable, noting the LDL threshold is in line with treatment thresholds in clinical guidelines and is consistent with the PBS restrictions of other third line agents for hypercholesteremia (i.e. evolocumab and inclisiran); however, it was noted that the primary evidence base was in statin intolerant patients only, with LDL ≥2.6 mmol/L with or without background lipid lowering therapy and that the treatment effect would likely attenuate with broader use, particularly among patients receiving statins or among patients with a lower baseline risk.

7.5 The PBAC considered that the proposed comparator of placebo as a proxy for standard of care (SoC) (i.e. ezetimibe monotherapy or ezetimibe in combination with maximally tolerated statin dose) was appropriate, as bempedoic acid would be given as an add-on therapy to SoC in clinical practice.

7.6 The PBAC noted that the submission was based on one head-to-head cardiovascular outcomes trial comparing bempedoic acid plus standard of care to placebo plus standard of care in adult patients with ASCVD or at high risk for ASCVD who were statin intolerant (CLEAR OUTCOMES). The PBAC noted evidence from the key trial was supported by 4 additional head-to-head trials comparing lipid outcomes for

bempedoic acid versus placebo in adults with uncontrolled hypercholesterolaemia in mixed populations with varying levels of background lipid lowering therapies (CLEAR HARMONY, CLEAR WISDOM, CLEAR SERENITY, CLEAR TRANQUILITY), and one head-to-head trial of bempedoic acid with ezetimibe FDC versus bempedoic acid alone, ezetimibe alone or placebo (Ballantyne 2020) in patients at high risk of cardiovascular disease due to ASCVD, HeFH or multiple cardiovascular disease risk factors. The PBAC noted, form the CLEAR OUTCOMES trial that bempedoic acid significantly reduced the risk of the primary composite endpoint of MACE-4 (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or coronary revascularisation) compared with placebo (11.7% vs 13.3%; HR: 0.87, 95% confidence interval [CI]: 0.79, 0.96), corresponding to an absolute reduction of 1.6% by Year 3 and 2.0% by Year 5. The PBAC also noted that treatment with bempedoic acid was associated with a significant reduction in the risk of MACE-3 (cardiovascular death, non-fatal MI, or non-fatal stroke) compared to placebo (8.2% vs 9.5%; HR: 0.85, 95% CI: 0.76, 0.96). The PBAC noted that bempedoic acid also lowered LDL by approximately 21% relative to placebo at 6 months, with broadly consistent LDL reductions across primary and secondary prevention subgroups.

7.7 The PBAC noted that the proposed PBS population was broader and clinically different from the population of the CLEAR OUTCOMES trial, with a lower LDL threshold and inclusion of patients receiving maximally tolerated statins. The PBAC considered that this difference led to uncertainty regarding the likely absolute benefit in clinical practice. The PBAC also noted that the magnitude of benefit associated with the combined use of bempedoic acid and statins was uncertain, given that both treatments share the same inhibitory pathway and data from the supportive trials suggest smaller LDL treatment effects for bempedoic acid with increasing statin intensity. Overall, the PBAC considered that the absolute benefits observed in the CLEAR OUTCOMES trial were likely to overestimate the benefits expected in the PBS population.

7.8 The PBAC noted that the proportions of patients reporting treatment emergent adverse events were generally consistent between treatment arms in the CLEAR OUTCOMES trial, with the exception of treatment related adverse events which were observed for 20.5% of patients in the bempedoic acid arm and 17.0% in the placebo arm. The PBAC noted that the overall incidence of hepatic enzyme abnormalities or elevations, cholelithiasis-related adverse events, and renal impairment related adverse events were numerically higher in the bempedoic acid arm compared with placebo. The PBAC considered that the claim of inferior comparative safety was reasonable.

7.9 The PBAC noted the submission presented a cost-utility analysis to support the cost-effectiveness of bempedoic acid versus placebo (as a proxy for SoC) based on the CLEAR OUTCOMES trial with additional modelled data. The PBAC noted that the economic evaluation provided separate analyses for the primary and secondary prevention populations and advised that these were preferred over the mixed population given the substantial differences in cardiovascular risk between these two

populations. The PBAC noted that the economic model was subject to substantial uncertainty, with key uncertainties biasing results in favour of bempedoic acid. The PBAC noted the main economic uncertainty related to extrapolating cardiovascular outcomes from the CLEAR OUTCOMES trial to the proposed PBS population. The CLEAR OUTCOMES trial enrolled statin-intolerant patients likely to be at higher baseline cardiovascular risk than the broader proposed PBS population, which has lower LDL thresholds, potentially lower baseline risk and different background therapy. The PBAC noted the Pre-PBAC Response indicated that it would be difficult to estimate how baseline risk was impacted by lowering the LDL threshold from 2.6 mmol/L to 1.8 mmol/L (see paragraph 6.84), however, the Committee considered that it would have been more appropriate for the model to account for differences in baseline cardiovascular risk and the resulting downstream treatment effects associated with different baseline LDL levels, consistent with the previous consideration of evolocumab (evolocumab, Public Summary Document [PSD], July 2022 PBAC meeting).

7.10 The PBAC noted the Pre-PBAC Response provided a revised economic model with revisions addressing a number of issues raised by the Sub-Committees (paragraphs 6.83–6.89). However, the PBAC considered that these analyses remained subject to considerable uncertainty and likely overestimated the cost-effectiveness of bempedoic acid. The PBAC advised the economic model should incorporate higher treatment discontinuation rates to better reflect use in a non-trial setting. The PBAC agreed with the Sub-Committees that ideally discontinuation would be modelled as time dependent, with higher rates applied early in treatment. The PBAC also considered that health state costs should decline over time rather than remain constant and would ideally approach event-free health state costs.

7.11 The PBAC recalled that acceptable incremental cost-effectiveness ratios (ICERs) in similar therapeutic areas have generally ranged from ≤$15,000 to $35,000 per quality adjusted life year (QALY) gained (para 5.5, icosapent ethyl PSD, March 2024 PBAC meeting; para 7.11, evolocumab PSD, July 2022 PBAC meeting). The PBAC considered that a price reduction would likely be required for bempedoic acid to be considered cost-effective with a revised model.

7.12 The PBAC noted that the Pre-PBAC Response provided revised financial estimates that incorporated amendments consistent with the Sub-Committee's advice. The PBAC considered that the revised estimates more accurately reflected the expected utilisation of listing bempedoic acid on the PBS. However, the PBAC noted that, in estimating the eligible patient population, the Response retained the proportion of ezetimibe use attributed to patients who are statin intolerant or receiving a maximally tolerated statin dose. The PBAC noted arguments made in the Pre-PBAC Response that not all ezetimibe prescriptions were consistent with the 2020–2024 PBS restriction, noting that DUSC had previously considered 35.8% of ezetimibe use to be outside the PBS listing. The PBAC considered this remained uncertain and retaining this adjustment may underestimate the financial estimates.

7.13 With respect to the proposed restrictions, the PBAC considered the following:

- The PBAC noted that the proposed definition of high-risk differed from the CLEAR OUTCOMES trial but was broadly aligned with the PBS listing for dapagliflozin. The PBAC considered the definition was likely reasonable, but again noting it reduced the applicability of the CLEAR OUTCOMES trial to the proposed PBS population.
- The PBAC noted that the definitions of statin intolerance in the requested restriction were stricter than the eligibility criteria of the CLEAR OUTCOMES trial. The PBAC considered that the definitions were likely reasonable and broadly consistent with the evolocumab PBS listing but noted a risk of use beyond the proposed definitions.
- The inclusion of Aboriginal and Torres Strait Islander people without additional risk factors (other than LDL >1.8 mmol/L) was likely reasonable.
- It would be reasonable for general practitioners to prescribe initial and continuing treatment of bempedoic acid without prior specialist consultation.
- The PBAC advised that a response criterion was not required.

7.14 The PBAC considered that any future resubmission for bempedoic acid should include a proposal for a risk sharing agreement and adequately address the outstanding issues with the economic evaluation and financial estimates identified in these minutes. The resubmission may be lodged at any future standard PBAC submission due date through the standard re-entry pathway.

7.15 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.