

**4.01 EVOLOCUMAB,
Injection 420 mg in 3.5 mL single use pre-filled
cartridge,
Injection 140 mg in 1 mL single use pre-filled pen,
Repatha[®],
Amgen Australia Pty Ltd**

1 Purpose of Application

- 1.1 The minor resubmission sought an Authority Required listing for evolocumab for the treatment of non-familial hypercholesterolaemia (non-FH) in patients with atherosclerotic cardiovascular disease (ASCVD) and additional high-risk factors. The minor resubmission also sought an extension of the current Authority Required listing of evolocumab for the treatment of familial hypercholesterolaemia (FH) to include patients with symptomatic ASCVD or homozygous FH who have an LDL level between 2.6 and 3.3 mmol/L despite optimised treatment with statins and ezetimibe.
- 1.2 The minor resubmission made the following changes, which were requested by the PBAC in its July 2019 deferral of evolocumab:
- a revised restriction based on the PBAC's July 2019 advice;
 - a [REDACTED] % price reduction, which resulted in an incremental cost-effectiveness ratio (ICER) of less than \$15,000 - \$45,000 per QALY using the revised base case parameters requested by the July 2019 PBAC;
 - this lower price was also proposed to apply to the additional FH populations with LDL-c levels between 2.6 and 3.3 mmol/L;
 - revised the financial estimates to incorporate the reduced price; and
 - a risk share arrangement (RSA) was proposed with a [REDACTED] rebate over the caps.

2 Requested listing

- 2.1 The requested listing was based on the PBAC's advice from its previous consideration of evolocumab. The resubmission also requested grandfather listings (discussed further below).
- 2.2 The requested listings for the non-FH population, as proposed by the resubmission, are outlined below. The proposed amendments to the existing heterozygous familial hypercholesterolaemia (he-FH) and homozygous familial hypercholesterolaemia (ho-

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FH) restrictions (including grandfather restrictions), as proposed by the resubmission, are also outlined below.

2.3 Grey-shading indicates differences compared with the previous submission for non-FH, or to the existing listing for FH. The restriction recommended by the PBAC is outlined in section 6.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Published (Effective) Dispensed price for maximum quantity	Proprietary name and manufacturer
EVOLOCUMAB, 140 mg/mL injection, 1 mL injection device	2	2	5	\$488.95 (\$ [REDACTED] ^a)	Repatha® Amgen
EVOLOCUMAB, 420 mg/mL injection, 3.5 mL injection device	1	1	5	\$529.68 (\$ [REDACTED] ^a)	Repatha® Amgen

Initial treatment

Category/ Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Hypercholesterolaemia
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	<p>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 2.6 millimoles per litre</p> <p>AND Patients must have atherosclerotic disease in two or more vascular territories (as per the symptomatic atherosclerotic cardiovascular disease criteria); OR Patient must have severe multivessel coronary heart disease defined as at least 40% 50% stenosis in at least two large vessels; OR Patient must have had at least two major cardiovascular events (i.e. myocardial infarction, unstable angina, stroke or unplanned revascularisation) in the previous 5 years; OR Patient must have diabetes mellitus with microalbuminuria; OR Patient must have diabetes mellitus and be aged 60 years of more; OR Patient must be an Aboriginal or Torres Strait Islander with diabetes mellitus; OR Patient must have a Thrombolysis in Myocardial Infarction (TIMI) Risk Score for Secondary Prevention (TRS2°P); of four or higher;</p>

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	<p>AND Statin tolerant: Patient must have been treated with the maximum recommended and tolerated dose of atorvastatin or rosuvastatin according to the TGA-approved Product Information for at least 3 months in conjunction with dietary therapy and exercise; OR</p> <p>Statin intolerant/contraindicated: 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,</p> <p>AND Patient must have been treated with ezetimibe for at least 3 months.</p>
Treatment criteria:	Must be treated by or in consultation with a specialist physician.
Prescriber Instructions	<p>Symptomatic atherosclerotic cardiovascular disease is defined as:</p> <p>Symptomatic coronary artery disease (prior MI <u>or</u> prior revascularisation procedure <u>or</u> angina associated with demonstrated significant coronary artery disease ($\geq 50\%$ stenosis in ≥ 1 coronary artery on imaging <u>or</u> positive functional testing e.g. myocardial perfusion scanning or Stress Echocardiography).</p> <p>Symptomatic cerebrovascular disease (prior ischaemic stroke <u>or</u> revascularisation procedure <u>or</u> transient ischaemic attack associated with $\geq 50\%$ stenosis in ≥ 1 cerebral arteries on imaging).</p> <p>Symptomatic peripheral arterial disease (prior acute ischaemic event due to atherosclerosis <u>or</u> prior revascularisation procedure <u>or</u> symptoms of ischaemia with evidence of significant peripheral artery disease ($\geq 50\%$ stenosis in ≥ 1 peripheral artery on imaging)).</p> <p>A clinically important product-related adverse event is defined as follows: (i) Severe myalgia (muscle symptoms without creatine kinase elevation) which is proven to be temporally associated with statin treatment; or (ii) Myositis (clinically important creatine kinase elevation, with or without muscle symptoms) demonstrated by results twice the upper limit of normal on a single reading or a rising pattern on consecutive measurements and which is unexplained by other causes; or (iii) Unexplained, persistent elevations of serum transaminases (greater than 3 times the upper limit of normal) during treatment with a statin.</p> <p>The date of the consultation with a specialist physician must be no more than 6 months prior to the application date. The full name of the specialist physician consulted and the date of consultation are to be provided at the time of application.</p> <p>The qualifying LDL cholesterol level must be provided at the time of application and must be no more than 2 months old.</p> <p>The physician must attempt to treat the patient with the maximum recommended dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily).</p> <p>If treatment with atorvastatin or rosuvastatin results in development of a clinically important product-related adverse event resulting in treatment withdrawal, the patient must be treated with the alternative statin (atorvastatin or rosuvastatin). This retrial should occur after a washout</p>

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	<p>period of at least 1 month, or if the creatine kinase (CK) level is elevated retriial should not occur until CK has returned to normal.</p> <p>In the event of a trial of an alternative statin, it is recommended that the patient is started with the minimum dose of statin in conjunction with ezetimibe. The dose of the alternative statin should be increased not more often than every 4 weeks until the maximum tolerated dose has been reached or target LDL-c has been achieved.</p> <p>At the time of application, one of the following must be provided:</p> <p>(i) Confirmation that the patient was treated with atorvastatin 80 mg or rosuvastatin 40 mg for 3 months; or</p> <p>(ii) The doses and duration of treatment and adverse events experienced with trials with each of atorvastatin and rosuvastatin; or</p> <p>(iii) Confirmation that the patient is contraindicated to treatment with a statin as defined in the TGA-approved Product Information.</p> <p>a) The date of consultation and the full name of the specialist physician must be recorded in the patient's medical records; and</p> <p>b) The result of LDL cholesterol level and one of the following where appropriate: statin treatment details including agent, dose and treatment duration; or details of adverse event or contraindication to treatment with a statin as defined in the TGA-approved Product Information must be recorded in the patient's medical records.</p>
Administrative Advice	<p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply</p> <p>Authority applications for initial treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p>

^a As stated in the restriction box on page 2 of the minor submission. This value was not verified.

Continuing treatment

Category/ Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Hypercholesterolaemia
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition AND</p> <p>The treatment must be in conjunction with dietary therapy and exercise.</p>

Grandfather treatment

Category/ Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Hypercholesterolaemia
Treatment phase:	Grandfather treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing

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	<input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [insert listing date]</p> <p>AND</p> <p>The treatment must be in conjunction with dietary therapy and exercise</p> <p>AND</p> <p>Patient must have symptomatic atherosclerotic cardiovascular disease</p> <p>AND</p> <p>Patient must have an LDL cholesterol level in excess of 2.6 millimoles per litre</p> <p>AND</p> <p>Patients must have atherosclerotic disease in two or more vascular territories (as per the symptomatic atherosclerotic cardiovascular disease criteria); OR</p> <p>Patient must have severe multivessel coronary heart disease defined as at least 40% 50% stenosis in at least two large vessels; OR</p> <p>Patient must have had at least two major cardiovascular events (i.e. myocardial infarction, unstable angina, stroke or unplanned revascularisation) in the previous 5 years; OR</p> <p>Patient must have diabetes mellitus with microalbuminuria; OR</p> <p>Patient must have diabetes mellitus and be aged 60 years of more; OR</p> <p>Patient must be an Aboriginal or Torres Strait Islander with diabetes mellitus; OR</p> <p>Patient must have a Thrombolysis in Myocardial Infarction (TIMI) Risk Score for Secondary Prevention (TRS2°P); of four or higher;</p> <p>AND</p> <p>Statin tolerant:</p> <p>Patient must have been treated with the maximum recommended and tolerated dose of atorvastatin or rosuvastatin according to the TGA-approved Product Information for at least 3 months in conjunction with dietary therapy and exercise; OR</p> <p>Statin intolerant/contraindicated:</p> <p>Patient must have developed clinically important product-related adverse events necessitating withdrawal of statin treatment to trials of each of atorvastatin and rosuvastatin; OR</p> <p>Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information,</p> <p>AND</p> <p>Patient must have been treated with ezetimibe for at least 3 months.</p>
Treatment criteria:	Must be treated by or in consultation with a specialist physician.
Prescriber Instructions	<p>Symptomatic atherosclerotic cardiovascular disease is defined as:</p> <p>Symptomatic coronary artery disease (prior MI <u>or</u> prior revascularisation procedure <u>or</u> angina associated with demonstrated significant coronary artery disease ($\geq 50\%$ stenosis in ≥ 1 coronary artery on imaging <u>or</u> positive functional testing e.g. myocardial perfusion scanning or Stress Echocardiography).</p> <p>Symptomatic cerebrovascular disease (prior ischaemic stroke <u>or</u> revascularisation procedure <u>or</u> transient ischaemic attack associated with $\geq 50\%$ stenosis in ≥ 1 cerebral arteries on imaging).</p> <p>Symptomatic peripheral arterial disease (prior acute ischaemic event due to atherosclerosis <u>or</u> prior revascularisation procedure <u>or</u> symptoms of ischaemia with</p>

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	<p>evidence of significant peripheral artery disease ($\geq 50\%$ stenosis in ≥ 1 peripheral artery on imaging).</p> <p>A clinically important product-related adverse event is defined as follows:</p> <ul style="list-style-type: none"> (i) Severe myalgia (muscle symptoms without creatine kinase elevation) which is proven to be temporally associated with statin treatment; or (ii) Myositis (clinically important creatine kinase elevation, with or without muscle symptoms) demonstrated by results twice the upper limit of normal on a single reading or a rising pattern on consecutive measurements and which is unexplained by other causes; or (iii) Unexplained, persistent elevations of serum transaminases (greater than 3 times the upper limit of normal) during treatment with a statin. <p>The date of the consultation with a specialist physician must be no more than 6 months prior to the date of evolocumab initiation. The full name of the specialist physician consulted and the date of consultation are to be provided at the time of application.</p> <p>The qualifying LDL cholesterol level must be provided at the time of application and must be no older than 2 months prior to the date of evolocumab initiation.</p> <p>The physician must attempt to treat the patient with the maximum recommended dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily).</p> <p>If treatment with atorvastatin or rosuvastatin results in development of a clinically important product-related adverse event resulting in treatment withdrawal, the patient must be treated with the alternative statin (atorvastatin or rosuvastatin). This retri al should occur after a washout period of at least 1 month, or if the creatine kinase (CK) level is elevated retri al should not occur until CK has returned to normal.</p> <p>In the event of a trial of an alternative statin, it is recommended that the patient is started with the minimum dose of statin in conjunction with ezetimibe. The dose of the alternative statin should be increased not more often than every 4 weeks until the maximum tolerated dose has been reached or target LDL-c has been achieved.</p> <p>At the time of application, one of the following must be provided:</p> <ul style="list-style-type: none"> (i) Confirmation that the patient was treated with atorvastatin 80 mg or rosuvastatin 40 mg for 3 months; or (ii) The doses and duration of treatment and adverse events experienced with trials with each of atorvastatin and rosuvastatin; or (iii) Confirmation that the patient is contraindicated to treatment with a statin as defined in the TGA-approved Product Information. (iv) Date of evolocumab initiation. <ul style="list-style-type: none"> a) The date of consultation and the full name of the specialist physician must be recorded in the patient's medical records; and b) The result of LDL cholesterol level and one of the following where appropriate: statin treatment details including agent, dose and treatment duration; or details of adverse event or contraindication to treatment with a statin as defined in the TGA-approved Product Information must be recorded in the patient's medical records. <p>A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.</p>
<p>Administrative Advice</p>	<p>No increase in the maximum number of repeats may be authorised.</p>

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	<p>Special Pricing Arrangements apply</p> <p>Authority applications for initial treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p>
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He-FH listing

Category/ Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Familial heterozygous hypercholesterolaemia
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	<p>The treatment must be in conjunction with dietary therapy and exercise, AND The condition must have been confirmed by genetic testing; OR The condition must have been confirmed by a Dutch Lipid Clinic Network Score of at least 6, AND Patient must have an LDL cholesterol level in excess of 2.6 millimoles per litre in the presence of symptomatic atherosclerotic cardiovascular disease; OR Patient must have an LDL cholesterol level in excess of 5 millimoles per litre, AND Patient must have been treated with the maximum recommended and/or tolerated dose of atorvastatin or rosuvastatin according to the TGA-approved Product Information for at least 3 months in conjunction with dietary therapy and exercise; 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 3 months in conjunction with dietary therapy and exercise.</p>
Treatment criteria:	Must be treated by or in consultation with a specialist physician.
Prescriber Instructions	<p>A clinically important product-related adverse event is defined as follows:</p> <p>(i) Severe myalgia (muscle symptoms without creatine kinase elevation) which is proven to be temporally associated with statin treatment; or</p> <p>(ii) Myositis (clinically important creatine kinase elevation, with or without muscle symptoms) demonstrated by results twice the upper limit of normal on a single reading or a rising pattern on consecutive measurements and which is unexplained by other causes; or</p> <p>(iii) Unexplained, persistent elevations of serum transaminases (greater than 3 times the upper limit of normal) during treatment with a statin.</p> <p>Symptomatic atherosclerotic cardiovascular disease is defined as:</p> <p>(i) the presence of symptomatic coronary artery disease; or</p> <p>(ii) the presence of symptomatic cerebrovascular disease; or</p>

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	<p>(iii) the presence of symptomatic peripheral vascular disease.</p> <p>The date of the consultation with a specialist physician must be no more than 6 months prior to the application date. The full name of the specialist physician consulted and the date of consultation are to be provided at the time of application.</p> <p>The qualifying LDL cholesterol level must be provided at the time of application and must be no more than 2 months old.</p> <p>The physician must attempt to treat the patient with the maximum recommended dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily).</p> <p>If treatment with atorvastatin or rosuvastatin results in development of a clinically important product-related adverse event resulting in treatment withdrawal, the patient must be treated with the alternative statin (atorvastatin or rosuvastatin). This retrial should occur after a washout period of at least 1 month, or if the creatine kinase (CK) level is elevated retrial should not occur until CK has returned to normal.</p> <p>In the event of a trial of an alternative statin, it is recommended that the patient is started with the minimum dose of statin in conjunction with ezetimibe. The dose of the alternative statin should be increased not more often than every 4 weeks until the maximum tolerated dose has been reached or target LDL-c has been achieved.</p> <p>At the time of application, one of the following must be provided:</p> <ul style="list-style-type: none"> (i) Confirmation that the patient was treated with atorvastatin 80 mg or rosuvastatin 40 mg for 3 months; or (ii) The doses and duration of treatment and adverse events experienced with trials with each of atorvastatin and rosuvastatin; or (iii) Confirmation that the patient is contraindicated to treatment with a statin as defined in the TGA-approved Product Information. <ul style="list-style-type: none"> a) The date of consultation and the full name of the specialist physician must be recorded in the patient's medical records; and b) The result of LDL cholesterol level and one of the following where appropriate: statin treatment details including agent, dose and treatment duration; or details of adverse event or contraindication to treatment with a statin as defined in the TGA-approved Product Information must be recorded in the patient's medical records; and c) The qualifying Dutch Lipid Clinic Network Score or a result of genetic testing must be recorded in the patient's medical records.
<p>Administrative Advice</p>	<p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply</p> <p>Authority applications for initial treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p>

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Category/ Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Familial heterozygous hypercholesterolaemia
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND The treatment must be in conjunction with dietary therapy and exercise.

He-FH grandfather listing

Category/ Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Familial heterozygous hypercholesterolaemia
Treatment phase:	Grandfather treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [insert listing date] AND The treatment must be in conjunction with dietary therapy and exercise, AND The condition must have been confirmed by genetic testing; OR The condition must have been confirmed by a Dutch Lipid Clinic Network Score of at least 6, AND Patient must have an LDL cholesterol level in excess of 2.6 millimoles per litre in the presence of symptomatic atherosclerotic cardiovascular disease; OR Patient must have an LDL cholesterol level in excess of 5 millimoles per litre, AND Patient must have been treated with the maximum recommended and tolerated dose of atorvastatin or rosuvastatin according to the TGA-approved Product Information for at least 3 months in conjunction with dietary therapy and exercise; 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 3 months in conjunction with dietary therapy and exercise.

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<p>Treatment criteria:</p>	<p>Must be treated by or in consultation with a specialist physician.</p>
<p>Prescriber Instructions</p>	<p>A clinically important product-related adverse event is defined as follows:</p> <ul style="list-style-type: none"> (i) Severe myalgia (muscle symptoms without creatine kinase elevation) which is proven to be temporally associated with statin treatment; or (ii) Myositis (clinically important creatine kinase elevation, with or without muscle symptoms) demonstrated by results twice the upper limit of normal on a single reading or a rising pattern on consecutive measurements and which is unexplained by other causes; or (iii) Unexplained, persistent elevations of serum transaminases (greater than 3 times the upper limit of normal) during treatment with a statin. <p>Symptomatic atherosclerotic cardiovascular disease is defined as:</p> <ul style="list-style-type: none"> (i) the presence of symptomatic coronary artery disease; or (ii) the presence of symptomatic cerebrovascular disease; or (iii) the presence of symptomatic peripheral vascular disease. <p>The date of the consultation with a specialist physician must be no more than 6 months prior to the date of evolocumab initiation, to the application date. The full name of the specialist physician consulted and the date of consultation are to be provided at the time of application.</p> <p>The qualifying LDL cholesterol level must be provided at the time of application and must be no older than 2 months prior to the date of evolocumab initiation.</p> <p>The physician must attempt to treat the patient with the maximum recommended dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily).</p> <p>If treatment with atorvastatin or rosuvastatin results in development of a clinically important product-related adverse event resulting in treatment withdrawal, the patient must be treated with the alternative statin (atorvastatin or rosuvastatin). This retrial should occur after a washout period of at least 1 month, or if the creatine kinase (CK) level is elevated retrial should not occur until CK has returned to normal.</p> <p>In the event of a trial of an alternative statin, it is recommended that the patient is started with the minimum dose of statin in conjunction with ezetimibe. The dose of the alternative statin should be increased not more often than every 4 weeks until the maximum tolerated dose has been reached or target LDL-c has been achieved.</p> <p>At the time of application, one of the following must be provided:</p> <ul style="list-style-type: none"> (i) Confirmation that the patient was treated with atorvastatin 80 mg or rosuvastatin 40 mg for 3 months; or (ii) The doses and duration of treatment and adverse events experienced with trials with each of atorvastatin and rosuvastatin; or (iii) Confirmation that the patient is contraindicated to treatment with a statin as defined in the TGA-approved Product Information. (iv) Date of evolocumab initiation. <ul style="list-style-type: none"> a) The date of consultation and the full name of the specialist physician must be recorded in the patient's medical records; and b) The result of LDL cholesterol level and one of the following where appropriate: statin treatment details including agent, dose and treatment duration; or details of adverse event or contraindication to treatment with a statin as defined in the TGA-approved Product Information must be recorded in the patient's medical records; and c) The qualifying Dutch Lipid Clinic Network Score or a result of genetic testing must be recorded in the patient's medical records.

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	A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
Administrative Advice	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply Authority applications for initial treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Ho-FH listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Published Dispensed price for maximum quantity	Proprietary name and manufacturer
EVOLOCUMAB, 140 mg/mL injection, 1 mL injection device	3	3	5	\$730.84	Repatha® Amgen
EVOLOCUMAB, 420 mg/mL injection, 3.5 mL injection device	1	1	5	\$529.68	Repatha® Amgen

Category/ Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Familial homozygous hypercholesterolaemia
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	The treatment must be in conjunction with dietary therapy and exercise, AND The condition must have been confirmed by genetic testing; OR The condition must have been confirmed by a Dutch Lipid Clinic Network Score of at least 7, AND Patient must have an LDL cholesterol level in excess of 2.6 millimoles per litre, AND Patient must have been treated with the maximum recommended dose of atorvastatin or rosuvastatin according to the TGA-approved Product Information for at least 3 months in conjunction with dietary therapy and exercise; OR Patient must have developed a clinically important product-related adverse event necessitating withdrawal of statin treatment; OR Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information
Treatment criteria:	Must be treated by or in consultation with a specialist physician.
Prescriber Instructions	A clinically important product-related adverse event is defined as follows:

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	<p>(i) Severe myalgia (muscle symptoms without creatine kinase elevation) which is proven to be temporally associated with statin treatment; or</p> <p>(ii) Myositis (clinically important creatine kinase elevation, with or without muscle symptoms) demonstrated by results twice the upper limit of normal on a single reading or a rising pattern on consecutive measurements and which is unexplained by other causes; or</p> <p>(iii) Unexplained, persistent elevations of serum transaminases (greater than 3 times the upper limit of normal) during treatment with a statin.</p> <p>The date of the consultation with a specialist physician must be no more than 6 months prior to the application date. The full name of the specialist physician consulted and the date of consultation are to be provided at the time of application.</p> <p>The qualifying LDL cholesterol level must be provided at the time of application and must be no more than 2 months old.</p> <p>The physician must attempt to treat the patient with the maximum recommended and/or tolerated dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily).</p> <p>With the exception of the situation where the patient is contraindicated to treatment with a statin, the agent, dose and duration of statin treatment must be provided at the time of application. Contraindication to treatment with a statin is as defined in the TGA-approved Product Information.</p> <p>At the time of application, one of the following must be provided:</p> <p>(i) Confirmation that the patient was treated with atorvastatin 80 mg or rosuvastatin 40 mg for 3 months; or</p> <p>(ii) The doses and duration of treatment and adverse events experienced with trials with each of atorvastatin and rosuvastatin; or</p> <p>(iii) Confirmation that the patient is contraindicated to treatment with a statin as defined in the TGA-approved Product Information.</p> <p>a) The date of consultation and the full name of the specialist physician must be recorded in the patient's medical records; and</p> <p>b) The result of LDL cholesterol level and one of the following where appropriate: statin treatment details including agent, dose and treatment duration; or details of adverse event or contraindication to treatment with a statin as defined in the TGA-approved Product Information must be recorded in the patient's medical records; and</p> <p>c) The qualifying Dutch Lipid Clinic Network Score or a result of genetic testing must be recorded in the patient's medical records.</p>
<p>Administrative Advice</p>	<p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply</p> <p>Authority applications for initial treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p>

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Category/ Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Familial homozygous hypercholesterolaemia
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND The treatment must be in conjunction with dietary therapy and exercise.

Ho-FH grandfather listing

Category/ Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Familial homozygous hypercholesterolaemia
Treatment phase:	Grandfather treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [insert listing date] AND The treatment must be in conjunction with dietary therapy and exercise, AND The condition must have been confirmed by genetic testing; OR The condition must have been confirmed by a Dutch Lipid Clinic Network Score of at least 7, AND Patient must have an LDL cholesterol level in excess of 2.6 millimoles per litre, AND Patient must have been treated with the maximum recommended dose of atorvastatin or rosuvastatin according to the TGA-approved Product Information for at least 3 months in conjunction with dietary therapy and exercise; OR Patient must have developed a clinically important product-related adverse event necessitating withdrawal of statin treatment; OR Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information.
Treatment criteria:	Must be treated by or in consultation with a specialist physician.
Prescriber 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.

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	<p>The date of the consultation with a specialist physician must be no more than 6 months prior to the date of evolocumab initiation. The full name of the specialist physician consulted and the date of consultation are to be provided at the time of application.</p> <p>The qualifying LDL cholesterol level must be provided at the time of application and must be no older than 2 months prior to the date of evolocumab initiation.</p> <p>The physician must attempt to treat the patient with the maximum recommended and/or tolerated dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily).</p> <p>With the exception of the situation where the patient is contraindicated to treatment with a statin, the agent, dose and duration of statin treatment must be provided at the time of application. Contraindication to treatment with a statin is as defined in the TGA-approved Product Information.</p> <p>At the time of application, one of the following must be provided:</p> <ul style="list-style-type: none"> (i) Confirmation that the patient was treated with atorvastatin 80 mg or rosuvastatin 40 mg for 3 months; or (ii) The doses and duration of treatment and adverse events experienced with trials with each of atorvastatin and rosuvastatin; or (iii) Confirmation that the patient is contraindicated to treatment with a statin as defined in the TGA-approved Product Information. (iv) Date of evolocumab initiation. <ul style="list-style-type: none"> a) The date of consultation and the full name of the specialist physician must be recorded in the patient's medical records; and b) The result of LDL cholesterol level and one of the following where appropriate: statin treatment details including agent, dose and treatment duration; or details of adverse event or contraindication to treatment with a statin as defined in the TGA-approved Product Information must be recorded in the patient's medical records; and c) The qualifying Dutch Lipid Clinic Network Score or a result of genetic testing must be recorded in the patient's medical records. <p>A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.</p>
<p>Administrative Advice</p>	<p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply</p> <p>Authority applications for initial treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p>

2.4 At its July 2019 meeting, the PBAC considered that a telephone/electronic initial Authority would be appropriate, provided the specific entry criteria is explicitly addressed and the prescriber is told to retain the relevant documentation' (paragraph 2.12, evolocumab Public Summary Document (PSD), July 2019). Another option would be an electronic initial Authority through the new online PBS authorities system (with an alternative option of a written initial Authority to prevent accessibility issues), as the electronic system may be more rigorous with respect to capturing the entry criteria and reducing the risk of use outside the intended population. The pre-PBAC response stated that the electronic system 'is not routinely used by many prescribers' and that the sponsor 'supports the use of the electronic approval process only if this is in addition to the more traditional telephone

- approval'. The PBAC considered that a written/electronic authority would be more likely to minimise leakage than a telephone authority, but considered that a telephone/electronic initial Authority would be appropriate if the potential for use outside the restriction could be appropriately managed through an RSA based on financial estimates that reflect only the intended high-risk population (to a reasonable degree of confidence).
- 2.5 The minor resubmission also requested that the restriction level for the existing FH listings change from written to telephone/electronic for initiation, and from telephone/electronic to streamlined for continuation. The PBAC considered this was appropriate for consistency across the indications.
 - 2.6 The resubmission stated that reducing the LDL-c threshold from 3.3 to 2.6 mmol/L for the ho-FH listing expands access to ho-FH patients without ASCVD. The minor resubmission stated that there will be very few ho-FH patients with LDL-C above 2.6 mmol/L but below 3.3 mmol/L.
 - 2.7 Historically, the prescriber type for evolocumab for the ho-FH listing (for initiation) was, "Must be treated by or in consultation with a specialist physician". In March 2018, when evolocumab was recommended for listing in he-FH, the treatment criterion was changed to "Must be treated by a specialist physician" as a means of tightening the restriction for the larger he-FH population. The existing ho-FH listing was then changed accordingly in order to align the restrictions. The resubmission requested that, for all evolocumab initiation listings across all indications, a patient "Must be treated by or in consultation with a specialist physician". The PBAC considered that "Must be treated by a specialist physician" for initiation of treatment should remain for all indications, consistent with its previous advice.
 - 2.8 For the non-FH and he-FH listings, it is a requirement (in the clinical criteria) that the patient must have been treated with ezetimibe for at least 3 months. The PBAC noted that the intent of this criterion is that the ezetimibe trial be completed prior to the patient commencing treatment with evolocumab.
 - 2.9 Following on from the above point, the existing FH restrictions currently state that the LDL result must not be more than 2 months old, but do not state that it must be after 3 months' statin treatment. Hence, a patient could potentially trial a statin for 1 month, perform the LDL test (and meet restriction wording) then complete the 3 months' statin treatment. In order to clarify the intent, the PBAC considered the wording of the prescriber instructions should be adjusted to clarify that the qualifying LDL cholesterol level must be following 3 months treatment with ezetimibe and a statin.
 - 2.10 The pre-PBAC response stated that advice from the sponsor's advisory board was that 'it would be appropriate for symptomatic peripheral arterial disease (PAD) to be a standalone risk criterion'. This was originally proposed in the July 2019 submission, but was removed from the clinical criteria as the July 2019 PBAC considered that high

risk patients with symptomatic PAD would already be covered by other criteria. The pre-PBAC response stated ‘whilst many will be covered by the other criteria, the advisory board members considered that some may be missed’ and requested that the PBAC reconsider whether symptomatic PAD could be included in the clinical criteria to cater for a small number of very high risk patients who might not otherwise qualify. The PBAC reiterated that the vast majority of high risk patients with symptomatic PAD who are at high cardiovascular risk would already qualify under other criteria and considered that including symptomatic PAD as a standalone criterion would increase the risk of use in lower risk patients in whom evolocumab has not been shown to be cost-effective. The PBAC considered that the restriction should not include symptomatic PAD as a specific criterion. Should the sponsor identify any specific subgroups of patients with PAD who are at high cardiovascular risk but who are not included in the restriction, then a resubmission requesting listing in these patients may be appropriate.

- 2.11 The resubmission requested grandfather listings to facilitate access for patients who meet the new eligibility criteria, but who would initiate evolocumab prior to the PBS listing date (e.g. privately funded, or through clinical trials or compassionate access). The resubmission estimated there would be fewer than 10,000 grandfathered patients and stated that these patients are already included in the prevalence-based financial estimates and hence would not pose an additional cost to the PBS.
- 2.12 The resubmission proposed a change to the previously-recommended wording for the definition of statin tolerance: “Patient must have been treated with the maximum recommended ~~and~~ or tolerated dose of atorvastatin or rosuvastatin...”. The PBAC considered that this change was appropriate for both the new and existing listings.
- 2.13 In March 2019, alirocumab was recommended for listing for the treatment of patients with he-FH with the same restriction wording as evolocumab for this indication. The PBAC considered that any changes to the LDL criteria for alirocumab would require a submission, but that the wording changes clarifying the intent of specific criteria and changes to the restriction level should flow-on to the alirocumab listing for he-FH (PBAC recommended in March 2019, but not yet listed). Specifically, these changes are to:
 - clarify that the qualifying LDL cholesterol level must be following 3 months treatment with ezetimibe and a statin;
 - change ‘...maximum recommended dose of atorvastatin or rosuvastatin’ to ‘...maximum recommended or tolerated dose of atorvastatin or rosuvastatin’; and
 - change the restriction level for initial therapy from written to telephone/electronic.

3 Background

Registration status

- 3.1 The TGA approved indication for evolocumab is:
- to reduce the risk of cardiovascular events (myocardial infarction, stroke and coronary revascularisation) in adults with established cardiovascular disease in combination with an optimally dosed statin and/or other lipid-lowering therapies
 - for the treatment of adults with primary hypercholesterolaemia (including he-FH and non-familial hypercholesterolaemia) to reduce low-density lipoprotein cholesterol:
 - in combination with a statin or statin with other lipid lowering therapies, or
 - alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant
 - for the treatment of adults and adolescents aged 12 years and over with ho-FH in combination with other lipid- lowering therapies.
- 3.2 Evolocumab (140 mg injection) was listed on the PBS in December 2016 for the treatment of ho-FH. An additional presentation of evolocumab (420 mg injection using an automated dosing device) was PBS listed in November 2017 for the same indication. In November 2018, the listing was extended to also include he-FH with very high LDL levels and/or atherosclerotic disease.

Previous PBAC consideration

- 3.3 In July 2019, the PBAC deferred making a recommendation on the listing of evolocumab for non-FH patients with ASCVD and additional high-risk factors due to the high ICER. The PBAC also considered that the total financial impact was high and represented a significant opportunity cost for the Commonwealth.
- 3.4 The PBAC also deferred making a recommendation to extend the existing FH listing to include patients with LDL levels >2.6 mmol/L (from >3.3 mmol/L). However, the PBAC considered that, should evolocumab be considered cost-effective in the non-FH population, then the cost-effectiveness of evolocumab could be inferred for an expanded FH listing, at the same price as accepted for non-FH.
- 3.5 The outstanding matters of concern from the July 2019 meeting are summarised in the table below.

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Table 1: PBAC matters of concern in previous consideration (July 2019)

Matters of concern		How the resubmission addresses it
	(Paragraph 7.15) The PBAC advised that a minor resubmission would be required that addresses the following issues:	
Restriction	Include the updated restriction based on the PBAC's advice (i.e. per the amended restriction under Paragraph 2.1).	Addressed
Price + Model	A further price reduction would be required to achieve an ICER < \$██████ / QALY, using the pre-PBAC response economic model with a baseline LDL-c adjustment of 0.8 mmol/L. The PBAC advised that this lower price should also be applied to the additional FH population/s.	A █████% reduction to the DPMQ was proposed (from \$██████ in the previous pre-PBAC response to \$██████ in the current resubmission), which resulted in an ICER of \$██████ / QALY (with an LDL-c adjustment of 0.8 mmol/L, as requested by the PBAC).
Financial estimates	The financial estimates should be revised to reflect the lower price (derived from the economic model outlined above).	Addressed. However, the PBAC considered that other parameters in the financial estimates would require adjustment.
	An RSA with a █████ rebate above the caps would be required given the uncertain patient numbers and the potential for use outside the restriction.	Addressed

Source: Compiled by the Secretariat. Paragraph references refer to the July 2019 evolocumab PSD.

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item as it was a minor submission.

Consumer comments

4.2 The PBAC noted that no consumer comments were received for this item.

Economic analysis

4.3 The minor resubmission addressed the PBAC's previous concerns with the economic model, which were:

- correcting the magnitude of the difference in baseline LDL-c between FOURIER and the proposed PBS population from 0.93 to 0.8 mmol/L (per paragraph 7.8, evolocumab PSD, July 2019); and
- including a price reduction to achieve an ICER of less than \$15,000 - \$45,000 per QALY (a price of \$██████ per month was applied in the model).

4.4 All other parameters in the economic model were unchanged, compared with the model submitted in the July 2019 pre-PBAC response. The results are outlined in the table below.

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Table 2: Results of the economic evaluation presented in the minor resubmission

Outcome	Evolocumab	Placebo	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Life Years	[REDACTED]	[REDACTED]	[REDACTED]
Cost/LY	[REDACTED]	[REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Cost/QALY	[REDACTED]	[REDACTED]	\$ [REDACTED]
July 2019 pre-PBAC response	[REDACTED]	[REDACTED]	\$ [REDACTED] ^a

Source: Minor resubmission 'Evolocumab_Economic_Model_Aug19.xlsx'

^a Based on an LDL-c adjustment of 0.93 mmol/L. An ICER/QALY was \$ [REDACTED] if an LDL-c adjustment of 0.8 mmol/L was used (pre current model)

4.5 The minor resubmission’s model estimated an ICER of \$15,000 - \$45,000 per QALY for the base case ‘combined high risk’ population. The results of scenario analyses for each of the separate high-risk populations specified in the restriction are outlined in the table below.

Table 3: Scenario analyses for subgroups

		Evolocumab	Placebo	Increment	ICER
Base case: Combined high risk	Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
	QALY	[REDACTED]	[REDACTED]	[REDACTED]	
MI with multiple events	Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
	QALY	[REDACTED]	[REDACTED]	[REDACTED]	
MI with multivessel disease	Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
	QALY	[REDACTED]	[REDACTED]	[REDACTED]	
Diabetes	Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
	QALY	[REDACTED]	[REDACTED]	[REDACTED]	
Symptomatic PAD	Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
	QALY	[REDACTED]	[REDACTED]	[REDACTED]	
High Risk TIMI	Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
	QALY	[REDACTED]	[REDACTED]	[REDACTED]	

Source: Table 1 of the minor resubmission

Abbreviations: ICER = incremental cost-effectiveness ratio; MI = myocardial infarction; PAD = peripheral arterial disease; TIMI = Thrombolysis in Myocardial Infarction, QALY = quality adjusted life year

The redacted table shows ICERs in the range of \$15,000/QALY - \$45,000/QALY Benefits and costs (trial versus economic model)

4.6 The July 2019 resubmission was based on clinical evidence from the FOURIER trial, which had a median follow-up of 2.2 years and demonstrated a statistically significant reduction in myocardial infarctions (MIs), stroke and coronary revascularisation. The requested population and economic evaluation were based on a higher risk population than included in the FOURIER trial, and the economic evaluation included substantial extrapolation (25-year time horizon) and a mortality benefit.

4.7 While the FOURIER trial showed no difference in fatal CHD, the PBAC previously noted that evolocumab was associated with a 59% relative decrease in LDL-c levels

compared with placebo (95% CI: 58%, 60%). The PBAC considered that the benefit of LDL-c lowering has been clearly established (paragraph 7.5, evolocumab PSD, July 2019). Further, 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 a 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 (paragraph 7.9, evolocumab PSD, July 2019).

- 4.8 In its July 2019 consideration, the PBAC requested that the sponsor provide data on the number of cardiovascular deaths, MIs, strokes and other major cardiovascular events avoided in the economic model over the 25-year time horizon together with a comparison of the number of events avoided in the FOURIER trial (paragraph 7.12, evolocumab PSD, July 2019).

Table 4: Average events per patient in the trial versus the economic model

	FOURIER trial (median follow-up 2.2 years)			Economic model (over 25 years, undiscounted, higher risk than trial population)		
	Evolocumab	Placebo	Increment	Evolocumab	Placebo	Increment
Fatal CHD	1.8%	1.7%	0.10%	57.4%	67.1%	-9.67%
Life years (undiscounted)				15.7	14.6	1.1
Non-fatal CHD						
MI ('heart attack')	3.95%	5.4%	-1.45%	78.1%	98.3%	-20.14%
Stroke	1.59%	2.06%	-0.47%	29.8%	37.5%	-7.69%

Source: pp9-10 of the minor resubmission

- 4.9 The risk of events (and the incremental benefit of evolocumab) was substantially higher in the economic model than in the trial because the model was based on a longer timeframe and targeted patients at higher risk than in the trial (and patients are at increased risk of events as they age over the model time horizon). The PBAC considered that this highlights that, to be cost-effective, utilisation of evolocumab needs to be targeted to the intended high-risk population. Leakage outside this population, to lower risk patients, is likely to result in evolocumab not being cost-effective.

- 4.10 The minor resubmission stated that:

- The patients who will be eligible for treatment with evolocumab are at high risk of death from coronary heart disease and 67% of them currently are expected to die of this cause. Use of evolocumab is expected to reduce the risk of dying from coronary heart disease to 57%.
- Treatment with evolocumab is expected to add 1.1 years to a patients' lifetime.
- Over their lifetime, 1,000 patients on current treatments have an average of 67 heart attacks per year and this is expected to be reduced by 17 heart attacks per year if they were treated with evolocumab. For the same 1,000 patients, the

average annual rate of 26 strokes per year is expected to be reduced by 7 strokes per year.

- After a few years, the submission expected that about 40,000 patients would be treated with evolocumab each year. Over their lifetime, these patients are expected to avoid about a quarter of the annual number of heart attacks and strokes they would otherwise have had. This is an average of 700 heart attacks and 270 strokes avoided each year.

4.11 For every 1,000 patients treated with evolocumab and followed-up for 25 years, the economic evaluation estimated that there would be:

- evolocumab drug costs of \$ [REDACTED] (including treatment discontinuations);¹
- 100 fatal coronary heart disease (CHD) events avoided, resulting in an average of 1.1 life years gained or 11 life years per death avoided ²
- 200 non-fatal MIs avoided, which would save less than \$10 million in treatment costs;³ and
- 80 non-fatal strokes avoided, which would be associated with improved quality of life, and would save less than \$10 million in treatment costs⁴.

4.12 The PBAC re-iterated its previous consideration that the claims of superior comparative effectiveness and non-inferior safety versus placebo were reasonable (paragraphs 6.26-6.27, evolocumab PSD, July 2019).

Drug cost/patient/year: \$ [REDACTED] (while on treatment)

4.13 The estimated drug cost for evolocumab per patient per year was \$ [REDACTED] based on 10.56 scripts per year and an effective DPMQ for this indication of \$ [REDACTED] per month (the price per month applied in the minor resubmission's economic model).

4.14 This is lower than in the previous submission (July 2019 pre-PBAC response), wherein the estimated drug cost for evolocumab per patient per year was \$ [REDACTED] based on a cost/patient/month of \$ [REDACTED].

Weighted pricing proposal

4.15 The minor resubmission proposed a new published price across all indications (\$488.95 DPMQ for the 2*140 mg presentation) and a special pricing arrangement (SPA) with an indication-specific effective DPMQ of \$ [REDACTED] for the 2*140 mg presentation, which provides sufficient therapy for 28 days (equivalent to \$ [REDACTED] per

¹ Based on undiscounted drug costs. Source: row 528, columns AB to AD on 'Model' worksheet

² Based on cells E13 and E4 on 'Model' worksheet

³ Based on cell E15 on 'Model' worksheet (rounded). Costs are undiscounted and were calculated by setting the cost for fatal events and stroke to \$0. The Incremental cost for non-fatal MI was \$ [REDACTED] per patient resulting in a cost of \$ [REDACTED] for 1,000 patients.

⁴ Based on cell E16 on 'Model' worksheet (rounded). Costs are undiscounted and were calculated by setting the cost for fatal events and MI to \$0. The Incremental cost for stroke was \$ [REDACTED] per patient resulting in a cost of \$ [REDACTED] for 1,000 patients.

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calendar month⁵). The proposed DPMQ would equate to an indication-specific AEMP of \$ [REDACTED] per 140 mg injection (for the new non-FH listing and the additional FH populations).

- 4.16 The proposed indication-specific effective DPMQ of \$ [REDACTED] for the 2*140 mg presentation is lower than the effective DPMQ of \$ [REDACTED] for the existing listings⁶.
- 4.17 The minor resubmission proposed a weighted price across all indications. This was calculated based on [REDACTED]% to [REDACTED]% split between:
- the number of scripts agreed in the existing deeds for the FH listings ([REDACTED]%) versus
 - the number of scripts estimated for the proposed new non-FH listing and the additional patient population in the expanded FH listings ([REDACTED]%).
- 4.18 The minor resubmission’s calculations underpinning its proposed weightings are outlined in the table below. For the existing listings, the agreed estimates do not extend to Year 6, so these were calculated in the submission by assuming a constant growth rate from the previous year/s.

Table 5: Weighted price proportions: Number of scripts agreed for existing listing versus estimated new scripts (as estimated in the minor resubmission)

Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Script numbers: Existing Ho-FH listing – agreed estimates					
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED] ^a	[REDACTED] ^a	[REDACTED] ^a
Script numbers: Existing He-FH listing – agreed estimates					
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED] ^b
Script numbers: Total existing listings – agreed estimates					
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Script numbers: New ASCVD + additional FH – as estimated in minor resubmission (per Table 6 below)					
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated new scripts as a proportion of total agreed scripts for existing indications					
[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%

Source: Table 4, page 8 of the minor resubmission

^a Agreed estimates do not extend to Year 4, so these were calculated by the sponsor assuming a constant growth rate from the previous years ([REDACTED]% annual growth)

^b Agreed estimates do not extend to Year 6, so these were calculated by the sponsor assuming a constant growth rate from the previous 2 years ([REDACTED]% annual growth)

- 4.19 The PBAC considered that the pricing arrangements reinforce the need for a high degree of confidence in the estimated PBS usage for the new and expanded listings.
- 4.20 The lower indication-specific effective DPMQ (\$ [REDACTED] per month) was not proposed to apply to any new ho-FH patients with LDL-c between 2.6 and 3.3 mmol/L. The minor

⁵ This was the input value in the model and was based on a monthly cycle length (30.4 days per month) while the 2*140 mg presentation was assumed to provide 28 days of therapy.

⁶ The effective DPMQ for the existing listing was calculated based on the values in Table 3 of the submission (Commonwealth payment of \$ [REDACTED] with the new published price plus an average patient co-payment of \$13.77)

resubmission stated that this expanded listing in ho-FH patients will represent very few patients. Further, the pre-PBAC response stated ‘the number of true ho-FH patients is small (less than 10,000) and they have such high LDL-C levels that they would all qualify under the existing listing’. The PBAC agreed with the pre-PBAC response that few, if any, additional patients would be prescribed evolocumab as a result of this change. As such, the PBAC considered that the calculation of the weighted price would not need to incorporate any new ho-FH patients with LDL-c between 2.6 and 3.3 mmol/L within the new indication-specific lower DPMQ.

Estimated PBS usage & financial implications

4.21 The minor resubmission updated the financial estimates to account for the lower price, as shown in the table below. Compared with the previous submission, this was the only change made to the financial estimates.

Table 6: Estimated use and financial implications for the new listing (non-FH and additional FH patients) with effective prices corresponding to a [REDACTED] % rebate (as proposed in minor resubmission)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Non-FH patients treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Additional FH patients treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total additional patients	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
140mg syringe services	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
420mg cartridge services	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total additional services	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Cost to PBS/RPBS (less co-payments)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Previous submission ^a	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 6, page 9 of the minor resubmission

^a Cost to PBS/RPBS (less co-payments) estimated in the July 19 pre-PBAC response

4.22 The minor resubmission estimated a net effective cost to the PBS/RPBS for the new listings (non-FH and additional FH patients) of more than \$100 million in Year 6 of listing, with a total net effective cost to the PBS/RPBS of more than \$100 million over the first six years of listing.

4.23 These estimates were reduced from an estimated net effective cost to the PBS/RPBS of more than \$100 million over six years in the July 2019 pre-PBAC response. In July 2019, the PBAC considered that the total financial impact was high and considered that this represented a significant opportunity cost for the Commonwealth (paragraph 7.13, evolocumab PSD, July 2019).

4.24 The steps used in the minor resubmission to estimate patient numbers are outlined below.

Table 7: Estimation of patient numbers (new non-FH and additional FH patients)

	Value	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
New non-FH listing							
Number treated with ezetimibe in 2018	[A]						
Assumed annual growth rate	% [B]						
Predicted number of patients on ezetimibe							
% with symptomatic ASCVD	%						
Remove FH patients with LDL \geq 2.6							
% with additional risk factors	%						
% on ezetimibe \geq 3 months	91% [C]						
% with LDL-C > 2.6 mmol/L	%						
Uptake		%	%	%	%	%	%
Total number of non-FH patients							
Additional FH patients							
Australian population	[D]	25,873,480	26,301,274	26,727,025	27,147,199	27,562,195	27,970,435
FH prevalence	1 in 353						
Predicted prevalent population		73,296	74,508	75,714	76,904	78,080	79,236
Diagnosis rate	%	%	%	%	%	%	
Predicted number diagnosed							
% symptomatic	%						
% LDL > 2.6 mmol/L	%						
% LDL > 3.3 mmol/L	%						
Uptake	[E]	%	%	%	%	%	%
Total number of new FH patients							
Total new patients							

Source: Table 7, page 9 of the minor resubmission
 Values shaded grey are discussed in the table below. [Bracketed letters correspond with row numbers in Table 8]

The redacted table shows that at year 6, the estimated total number of patients was 10,000 – 50,000.

4.25 The cost-effectiveness of evolocumab relies on use being restricted to a high-risk population (refer to Table 4; the modelled population without evolocumab experienced an average of 1 heart attack and 0.4 strokes over their lifetime, with two-thirds of patients experiencing a fatal CHD event). The PBAC considered that the financial estimates, which are being used to inform an RSA, should represent this

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high-risk population and minimise the financial risk to the Commonwealth of use in lower-risk patients in whom evolocumab has not been shown to be cost-effective.

- 4.26 The July 2019 DUSC Advice stated that the financial estimates were uncertain, and uncertainties with the financial estimates are outlined in Table 8.

Table 8: Areas of uncertainty in the financial estimates

#	Description
New non-FH listing	
A	The number of patients on ezetimibe +/- statin (█%). The submission's estimate was based on a PBS 10% sample of the number of patients who received ezetimibe in the 12 months to September 2018. The July 2019 DUSC advice (p7) states 'Not all of these patients will have ASCVD as ezetimibe is more broadly reimbursed. The evaluator commented that the analysis of the PBS 10% sample data was poorly documented'. An analysis was undertaken by the DUSC Secretariat which found a lower estimate of 362,810 patients treated in 2018 based on a 10% PBS sample including all listings for the following drugs: ezetimibe, ezetimibe with simvastatin, rosuvastatin with ezetimibe and ezetimibe with atorvastatin.
B	Annual growth rate for symptomatic ASCVD (non-FH) (█%). The annual growth rate of █% was compounded over 7 years which resulted in an approximate doubling of patient numbers. The DUSC Secretariat calculated an annual growth rate for prevalent patients for all listings of ezetimibe, ezetimibe with simvastatin, rosuvastatin with ezetimibe and ezetimibe with atorvastatin of 5% in 2018.
C	Proportion of symptomatic ASCVD (non-FH) patients remaining on ezetimibe for more than 3 months (█%). The submission's estimate was based on a PBS 10% sample. The July 2019 DUSC advice (p10) states 'The evaluator (COM.193) commented there was insufficient information to validate this estimate'. The DUSC Secretariat examined the time on therapy for patients first initiating on the following drugs in 2017-18 with follow-up to 30 June 2019 using a 10% sample for ezetimibe, ezetimibe with simvastatin, rosuvastatin with ezetimibe and ezetimibe with atorvastatin. 80.1% of initiators were found to have three or more months of therapy.
Additional FH patients	
D	Inclusion of patients aged less than 25 years. DUSC (November 2017) considered the FH prevalence estimate of 1:353 was reasonable as this was based on the nationally representative AusDiab study. However, DUSC considered prevalence should be applied to the population aged 25 years or more to be consistent with AusDiab. The pre-PBAC response stated that the estimates 'allow for the adult only AusDiab population in the analysis with an adjustment to the ASCVD prevalence from 51% (as in Watts 2015) to █%. This methodology was unclear and was unlikely to have sufficiently accounted for the adult only population. It would have been more appropriate to adjust for the adult population in a more explicit manner. Further, the proportion of patients with symptomatic disease varied between 27% and 51% in the literature cited in the submission, so an adjustment of █% was appropriate for the whole FH population (all ages). The November 2017 commentary stated that "The resubmission noted that published estimates of coronary artery disease ranged from 43-51% in Australian familial hypercholesterolaemia populations. In addition, unpublished data included in the resubmission indicated that 27% of familial hypercholesterolaemia patients managed at an Australia lipid clinic had atherosclerotic disease. Based on the available information, the resubmission assumed that approximately █% of familial hypercholesterolaemia patients will have atherosclerotic disease (coronary artery disease, cerebrovascular disease and peripheral vascular disease)"(7.04.COM.110, evolocumab November 2017). Overall, the PBAC considered that there was a wide variation in available prevalence estimates and that, in the context of the uncertain financial estimates which are being used to inform subsidy caps, the proportion of FH patients with symptomatic ASCVD should remain at █% as this likely reflected the whole FH population (all ages). Further, the PBAC considered that the adult only population should be adjusted for in a more explicit manner by applying an FH prevalence rate of 1:353 to the population aged 25 years or more.
E	Treatment uptake assumptions for FH+ASCVD population. The assumed uptake rates of █% in Year 1 increasing to █% in Year 6 for patients with LDL-C of 2.6 to 3.3 mmol/L were higher than the uptake rates included in the November 2017 resubmission for patients with LDL-C > 3.3 mmol/L (█% in Year 1 increasing to █% in Year 6). The July 2019 DUSC (p5) advice stated "DUSC previously considered that the proposed uptake of evolocumab was overestimated compared to the uptake of injectable therapies in other chronic disease markets such as diabetes

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#	Description
	and osteoporosis (DUSC Advice November 2017, 7.04.DUSC ADV.6). Uptake rates may be lower among patients with LDL-C in the 2.6 to 3.3 mmol/L range ^a .
Both patient groups	
	Treatment compliance (88%). The compliance rate used by the submission (88%) aligned with persistence (the proportion discontinuing treatment) in the FOURIER trial, however this may not align with compliance and adherence (which includes missed doses etc), and may not reflect use outside a clinical trial setting. Compliance of 85% to PBS therapy was reported in the review of statin therapies (July 2012). The submission's assumed compliance rate of 88% was higher than the rate used in the November 2017 resubmission for patients with LDL-C > 3.3 mmol/L (85%). Treatment compliance may be lower among patients with LDL-C in the 2.6 to 3.3 mmol/L range.

Source: Based on the financial estimates spreadsheet and the July 2019 DUSC advice

4.27 The PBAC considered that the above uncertainties resulted in the minor resubmission's financial estimates (and hence the proposed caps) being overestimated. The impact of using the noted alternative assumptions is presented in Table 9, and results in a cost to the PBS/RPBS of more than \$100 million over six years (compared with more than \$100 million in the minor resubmission).

Table 9: Net cost to the PBS/RPBS using alternative assumptions as per Table 8 (for the new non-FH listing and additional FH patients)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
PBAC revised estimates	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Calculated based on 'Financial estimates_all listings with [REDACTED]% rebate.xlsx'

^a Changes to the financial estimates spreadsheet (Financial estimates_additional use only with [REDACTED]% rebate) were made on the 'Background and Assumptions' worksheet and were: [A] B39 was changed to 362,810; [B] B40:H40 changed to 5%; [C] B43 changed to 80.1%; [D] C31:H31 changed to: 17,701,025; 18,014,612; 18,325,590; 18,633,517; 18,937,442; 19,236,668; [E] C48:E48 changed to: [REDACTED]%; [REDACTED]%; [REDACTED]%; [F] B56:B57 changed to multiply for 85%.

4.28 The PBAC noted that the key driver of the difference between the resubmission's estimates and the revised estimates presented in Table 9 was the annual growth rate applied to the non-FH population. The PBAC noted that the resubmission's estimates of [REDACTED]% compounding annual growth led to a substantial increase in the eligible population over six years, and considered that such a high growth rate over an extended period of time was not reasonable. The PBAC considered that a 5% annual growth rate, consistent with the annual growth rate of ezetimibe (as used in the estimates in Table 9), was more likely. The PBAC noted this was still a high rate of growth, given the 5% annual growth rate was also compounding and would increase patient numbers by around 34% over the forward estimates (and there were additional inputs that would further increase patient numbers over time such as an increasing diagnosis rate, and increasing uptake over the forward estimates period).

4.29 The PBAC noted that another key driver of the difference was that the minor resubmission used a 10% PBS sample that was poorly documented to determine: the number of patients on ezetimibe; and the proportion of symptomatic ASCVD (non-FH) patients remaining on ezetimibe for more than 3 months. The PBAC considered that the analysis undertaken by the DUSC Secretariat (as used in the estimates in Table 9) should instead be the basis for the estimates.

4.30 Further, the PBAC considered that the other changes outlined in Table 8 were

appropriate, including that:

- patients aged less than 25 years should be explicitly excluded from the calculation of the prevalent population;
- uptake rates for the additional FH population should be consistent with those used in the November 2017 resubmission for patients with LDL-C > 3.3 mmol/L (■% in Year 1 increasing to ■% in Year 6); and
- a compliance rate of 85%, consistent with the rate reported in the review of statin therapies, was more appropriate than the rate used in the minor resubmission of 88%. The latter was based on the FOURIER trial and may not reflect use outside a clinical trial setting.

- 4.31 The pre-PBAC response stated that there were also areas for potential under-estimation, however the PBAC reiterated its previous advice that the financial estimates were high and uncertain, noting the previous DUSC advice (July 2019, p1) which outlined: that the multiple steps involved in the estimation of the non-FH population with numerous assumptions increases the risk of error; and the sources of uncertainty with the estimation of the additional FH population (including prevalence of disease, diagnosis rates, proportion of patients with LDL between 2.6 and 3.3 mmol/L, uptake rates and treatment compliance rates).
- 4.32 Given this high degree of uncertainty with the financial estimates, the PBAC considered that conservative assumptions would be required to provide a greater level of confidence that the utilisation estimates reflect only the high-risk population in order to ensure cost-effectiveness.

Financial Management – Risk Sharing Arrangements

- 4.33 The minor resubmission proposed an RSA with a ■ rebate over the caps.
For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

- 5.1 The PBAC recommended the Authority Required listing of evolocumab, but on the basis that it be available only in the circumstances where use is restricted to the treatment of:
- non-familial hypercholesterolaemia (non-FH) in patients with atherosclerotic cardiovascular disease (ASCVD), who have an LDL level greater than 2.6 mmol/L and additional high-risk factors; and
 - familial hypercholesterolaemia in patients with symptomatic ASCVD or homozygous FH (ho-FH), who have an LDL level between 2.6 and 3.3 mmol/L.
- The PBAC's recommendation for listing was based on, among other matters, its assessment, that the cost-effectiveness of evolocumab would be acceptable at the price proposed in the minor resubmission. The PBAC considered that the financial

impact would be lower than estimated in the resubmission, and that the risk of use outside the restriction would need to be managed with a Risk Sharing Arrangement (RSA).

- 5.2 The PBAC re-iterated that there is a moderate unmet clinical need, in a potentially large population, for patients with hypercholesterolaemia with high cardiovascular risk who are not adequately controlled with available lipid-lowering therapies.
- 5.3 The PBAC considered that, overall, the revised restriction had adequately defined the high-risk subgroups who would derive the most benefit from treatment with evolocumab.
- 5.4 The PBAC recommended the following changes to the restriction requested in the minor resubmission:
 - the treatment criterion for initiation of evolocumab should state “Must be treated by a specialist physician”; and
 - the LDL prescriber instructions should be adjusted to clarify that the qualifying LDL cholesterol level must be following 3 months treatment with ezetimibe and a statin.
- 5.5 The PBAC noted the resubmission requested grandfather listings to facilitate access for patients who meet the new eligibility criteria, but who would initiate evolocumab prior to the PBS listing date (e.g. privately funded, or through clinical trials or compassionate access). The resubmission estimated there would be fewer than 10,000 grandfathered patients and stated that these patients are already included in the prevalence-based financial estimates and hence would not pose an additional cost to the PBS. The PBAC considered this was appropriate.
- 5.6 The PBAC considered that evolocumab was associated with important clinical benefits in the intended high-risk population. The resubmission stated that patients who are eligible for evolocumab are at high cardiovascular risk, with 67% of eligible patients likely to die from coronary heart disease without evolocumab. Use of evolocumab is expected to reduce this risk to 57%.
- 5.7 The risk of cardiovascular events and the incremental benefit of evolocumab was substantially higher in the economic model than in the FOURIER trial (as outlined in Table 4), and one of the reasons was that the model targeted patients at higher risk than in the trial. The PBAC considered that this highlights that, to be cost-effective, utilisation of evolocumab needs to be targeted to the intended high-risk population.
- 5.8 The PBAC noted the resubmission had amended the economic model and adequately addressed the Committee’s previous concerns by: correcting the magnitude of the difference in baseline LDL-c between FOURIER and the proposed PBS population; and including a price reduction. The PBAC noted that these changes resulted in an ICER of less than \$15,000 - \$45,000 per QALY, and considered that evolocumab was cost-effective at the proposed price in the requested population.

- 5.9 The PBAC considered that the financial estimates, which are being used to inform an RSA, should reflect this high-risk population and minimise the financial risk to the Commonwealth of use in lower-risk patients in whom evolocumab has not been shown to be cost-effective. The PBAC noted that the pre-PBAC response had identified areas for potential under-estimation in the financial estimates. However, given the high degree of uncertainty in the financial estimates, the PBAC considered that conservative assumptions would be required to provide a greater level of confidence that the utilisation estimates reflect only the intended high-risk population in order to ensure cost-effectiveness.
- 5.10 Overall, the PBAC considered that the assumptions outlined in Table 8 and the estimates outlined in Table 9 (above) were the most realistic estimates of the financial impact of listing evolocumab for the reasons outlined in Paragraphs 4.28 to 4.30.
- 5.11 The PBAC considered that an RSA with a rebate for use above the caps would be required given the uncertain patient numbers and the potential for use outside the restriction. The PBAC considered that the subsidy cap should be based on the estimates outlined in Table 9 above (which result in a net cost to the PBS/RPBS of more than \$100 million over 6 years).
- 5.12 The PBAC noted that there is likely to be overlap between the populations covered by the current and new listings. As a result, it may be appropriate to implement a single RSA cap to encompass all evolocumab use across these indications. The PBAC further recalled that the current listings for evolocumab are subject to [REDACTED] rebate for any use beyond the financial caps. The PBAC considered that a similarly high rebate is likely to be required for these new listings due to the high and uncertain financial estimates.
- 5.13 The PBAC noted that the minor resubmission requested a weighted average effective price for evolocumab across the existing and new patient populations, and considered this was reasonable. The PBAC considered that, should the effective price be weighted across the two populations, the weighting applied should be consistent with the agreed final financial estimates across the two settings.
- 5.14 The PBAC considered that specific changes to the evolocumab he-FH restriction that clarify the intent of some of the clinical criteria and change the restriction level for initial therapy should also flow-on to alirocumab (which was recommended for listing in the he-FH population in March 2019) as outlined in paragraph 2.13.
- 5.15 The PBAC advised that evolocumab is not suitable for prescribing by nurse practitioners, consistent with the current PBS listing for evolocumab.
- 5.16 The PBAC advised that evolocumab should not be exempt from the Early Supply Rule, consistent with current PBS listing for evolocumab.
- 5.17 The PBAC did not recommend that evolocumab should be treated as interchangeable

on an individual patient basis with any other drug for the non-FH and expanded FH indications.

- 5.18 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically the PBAC found that the circumstances of its recommendation for evolocumab:
- a) Treatment with evolocumab is expected to provide a substantial and clinically relevant improvement in efficacy over alternative therapies with respect to its benefit of LDL-c lowering and reduction in major adverse cardiovascular events.
 - b) Treatment with evolocumab is not expected to address a high and urgent unmet clinical need because other subsidised therapies are available;
 - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 5.19 The PBAC advised that this submission would not meet the criteria for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

6 Recommended listing

Initial treatment (non-familial hypercholesterolaemia)

6.1 Add new non-familial hypercholesterolaemia with atherosclerotic cardiovascular disease indications as follows:

Name, restriction, manner of administration, form	Max. Qty (packs)	Max. Qty (units)	No. of repeats	PBS item code	Proprietary name and manufacturer
EVOLUCUMAB, 140 mg/mL injection, 1 mL pen device	2	2	5	11484K	Repatha® Amgen
EVOLUCUMAB, 420 mg/mL injection, 3.5 mL cartridge	1	1	5	11485L	Repatha® Amgen

Safety Net Rule Penalty Applies: Yes

Resupply Interval Days: 20

1) Restriction Summary [new] / Treatment of Concept: [new]

Concept ID:	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	Restriction Level / Method: <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Emergency/Electronic <input type="checkbox"/> Streamlined
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7608	Administrative Advice: Special Pricing Arrangements apply.
	Episodicity:[nil]
	Severity: [nil]
	Condition: Non-familial hypercholesterolaemia
new	PBS indication: Non-familial hypercholesterolaemia
	Treatment Phase: Initial treatment
7792	Clinical criteria:
7791	The treatment must be in conjunction with dietary therapy and exercise
	AND
new	Clinical criteria: Patient must have symptomatic atherosclerotic cardiovascular disease
	AND
new	Clinical criteria: Patient must have an LDL cholesterol level in excess of 2.6 millimoles per litre
	AND
new	Clinical criteria: Patient must have atherosclerotic disease in two or more vascular territories (coronary, cerebrovascular or peripheral vascular territories); or Patient must have severe multi-vessel coronary heart disease defined as at least 50% stenosis in at least two large vessels; or Patient must have had at least two major cardiovascular events (i.e. myocardial infarction, unstable angina, stroke or unplanned revascularisation) in the previous 5 years; or Patient must have diabetes mellitus with microalbuminuria; or Patient must have diabetes mellitus and be aged 60 years of more; or Patient must be an Aboriginal or Torres Strait Islander with diabetes mellitus; or Patient must have a Thrombolysis in Myocardial Infarction (TIMI) risk score for secondary prevention of 4 or higher
22912	Clinical criteria:

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edit 22837	Patient must have been treated with the maximum recommended <i>or tolerated</i> dose of atorvastatin or rosuvastatin according to the TGA-approved Product Information for at least 3 months in conjunction with dietary therapy and exercise; or
edit 22911	Patient must have developed a clinically important product-related adverse event necessitating withdrawal of statin treatment <i>to trials of each of atorvastatin and rosuvastatin</i> ; or
22839	Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information
	AND
22842	Clinical criteria:
22841	Patient must have been treated with ezetimibe for at least 3 months in conjunction with dietary therapy and exercise.
22846	Treatment criteria:
22845	Must be treated by a specialist physician.
edit 22877	Prescribing Instructions: The physician must attempt to treat the patient with the maximum recommended <i>or tolerated</i> dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily).
edit 22847	Prescribing Instructions: Symptomatic atherosclerotic cardiovascular disease is defined as: (i) the presence of symptomatic coronary artery disease (<i>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)</i>); or (ii) the presence of symptomatic cerebrovascular disease (<i>prior ischaemic stroke, revascularisation procedure, or transient ischaemic attack associated with 50% or greater stenosis in 1 or more cerebral arteries on imaging</i>); or (iii) the presence of symptomatic peripheral arterial disease (<i>prior acute ischaemic event due to atherosclerosis, prior revascularisation procedure, or symptoms of ischaemia with evidence of significant peripheral artery disease (50% or greater stenosis in 1 or more peripheral arteries on imaging)</i>).
edit 22876	Prescribing Instructions: The qualifying LDL cholesterol level <i>following at least 3 months treatment with ezetimibe and a statin (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)</i> must be documented in the patient's medical records and must be no more than 2 months old.
7840	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.
22878	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). This retreatment should occur after a washout period of at least 1 month, or if the creatine kinase (CK) level is elevated retreatment should not occur until CK has returned to normal.
22879	Prescribing Instructions: In the event of a trial of an alternative statin, it is recommended that the patient is started with the minimum dose of statin in conjunction with ezetimibe. The dose of the alternative statin should be increased not more often than every 4 weeks until the maximum tolerated dose has been reached or target LDL-c has been achieved.
New	Prescribing Instructions: One of the following must be documented in the patient's medical records: (i) Confirmation that the patient was treated with atorvastatin 80 mg or rosuvastatin 40 mg for 3 months; or (ii) The doses and duration of treatment and details of adverse events experienced with trials with each of atorvastatin and rosuvastatin; or

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	(iii) Confirmation that the patient is contraindicated to treatment with a statin as defined in the TGA-approved Product Information.
New (1)	Administrative Advice: Authority applications for initial treatment may be made by telephone to the Authority Prescription Applications 24 hour service on free call 1800 888 333 or via the Health Professional Online Services (HPOS) website.

Continuing treatment (non-familial hypercholesterolaemia)

2) Restriction Summary [new] / Treatment of Concept: [new]

Concept ID:	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	Restriction Level / Method: <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined [new code]
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7608	Administrative Advice: Special Pricing Arrangements apply.
	Episodicity:[nil]
	Severity: [nil]
	Condition: Non-familial hypercholesterolaemia
new	PBS indication: Non-familial hypercholesterolaemia
	Treatment Phase: Continuing treatment
11365	Clinical criteria:
11364	Patient must have previously received PBS-subsidised treatment with this drug for this condition.
	AND
7792	Clinical criteria:
7791	The treatment must be in conjunction with dietary therapy and exercise

Grandfather treatment (non-familial hypercholesterolaemia)

3) Restriction Summary [new] / Treatment of Concept: [new]

Concept ID:	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	Restriction Level / Method: <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Emergency/Electronic <input type="checkbox"/> Streamlined
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7608	Administrative Advice: Special Pricing Arrangements apply.
	Episodicity:[nil]
	Severity: [nil]
	Condition: Non-familial hypercholesterolaemia
new	PBS indication: Non-familial hypercholesterolaemia
	Treatment Phase: Grandfathered treatment
	Clinical criteria:
new	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [insert listing date]

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	AND
7792	Clinical criteria:
7791	The treatment must be in conjunction with dietary therapy and exercise
	AND
new	Clinical criteria: Patient must have symptomatic atherosclerotic cardiovascular disease
	AND
new	Clinical criteria: Patient must have had an LDL cholesterol level in excess of 2.6 millimoles per litre prior to starting treatment
	AND
new	Clinical criteria: Patient must have atherosclerotic disease in two or more vascular territories (coronary, cerebrovascular or peripheral vascular territories); or Patient must have severe multi-vessel coronary heart disease defined as at least 50% stenosis in at least two large vessels; or Patient must have had at least two major cardiovascular events (i.e. myocardial infarction, unstable angina, stroke or unplanned revascularisation) in the previous 5 years; or Patient must have diabetes mellitus with microalbuminuria; or Patient must have diabetes mellitus and be aged 60 years of more; or Patient must be an Aboriginal or Torres Strait Islander with diabetes mellitus; or Patient must have a Thrombolysis in Myocardial Infarction (TIMI) Risk Score for Secondary Prevention of 4 or higher;
22912	Clinical criteria:
edit 22837	Patient must have been treated with the maximum recommended <i>or tolerated</i> dose of atorvastatin or rosuvastatin according to the TGA-approved Product Information for at least 3 months in conjunction with dietary therapy and exercise; or
edit 22911	Patient must have developed a clinically important product-related adverse event necessitating withdrawal of statin treatment to <i>trials of each of atorvastatin and rosuvastatin</i> ; or
22839	Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information
	AND
22842	Clinical criteria:
22841	Patient must have been treated with ezetimibe for at least 3 months in conjunction with dietary therapy and exercise.
22846	Treatment criteria:
22845	Must be treated by a specialist physician.
new	Prescribing Instructions: The date of the patient's consultation with a specialist physician must have been no more than 6 months prior to initiating treatment with this drug. The full name of the specialist physician consulted and the date of consultation must be documented in the patient's medical records.
edit 22877	Prescribing Instructions: The physician must attempt to treat the patient with the maximum recommended <i>or tolerated</i> dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily).
New	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, 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)).
New	Prescribing Instructions:

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	The qualifying LDL cholesterol level following at least 3 months of treatment with ezetimibe and a statin (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 have been measured within 2 months prior to having started treatment with this drug.
7840	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.
New [22878 modified]	Prescribing Instructions: If treatment with atorvastatin or rosuvastatin resulted in development of a clinically important product-related adverse event resulting in treatment withdrawal, the patient must <i>have been</i> treated with the alternative statin (atorvastatin or rosuvastatin). This retrial should <i>have occurred</i> after a washout period of at least 1 month, or if the creatine kinase (CK) level was elevated retrial should not <i>have occurred</i> until CK has returned to normal.
edit 22907	Prescribing Instructions: In the event of a trial of an alternative statin, the dose of the alternative statin should <i>have been</i> increased not more often than every 4 weeks until the maximum tolerated dose has been reached or target LDL-c has been achieved. With the exception of the situation where the patient is contraindicated to treatment with a statin, the doses and duration of treatment and adverse events experienced with trials with each of atorvastatin and rosuvastatin must be provided at the time of application <i>documented in the patient's medical records</i> .
New	Prescribing Instructions: One of the following must be documented in the patient's medical records: (i) Confirmation that the patient was treated with atorvastatin 80 mg or rosuvastatin 40 mg for 3 months; or (ii) The doses and duration of treatment and details of adverse events experienced with trials with each of atorvastatin and rosuvastatin; or (iii) Confirmation that the patient is contraindicated to treatment with a statin as defined in the TGA-approved Product Information.
21046	Prescribing Instructions: A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.

He-FH listing – initiation

1.2 *Amend the existing initial treatment restriction in familial heterozygous hypercholesterolaemia as follows:*

- 1) *revise LDL-c eligibility threshold from 3.3 mmol/L to 2.6 mmol/L in concept ID: 22833;*
- 2) *clarify that the qualifying LDL cholesterol level must be following 3 months treatment with ezetimibe and a statin in concept ID: 22876; and*
- 3) *change ‘...maximum recommended dose of atorvastatin or rosuvastatin’ to ‘...maximum recommended or tolerated dose of atorvastatin or rosuvastatin’ in concept IDs: 22387 & 22877; and*
- 4) *change the Authority approval method from ‘In writing’ to ‘telephone/emergency/electronic’*

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Name, restriction, manner of administration, form	Max. Qty (packs)	Max. Qty (units)	No. of repeats	PBS item code	Proprietary name and manufacturer
EVOLUCUMAB, 140 mg/mL injection, 1 mL pen device	2	2	5	11484K	Repatha® Amgen
EVOLUCUMAB, 420 mg/mL injection, 3.5 mL cartridge	1	1	5	11485L	Repatha® Amgen

Restriction Summary 8086 / ToC: 8078: Authority Required

Concept ID	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	Restriction Level / Method: <input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Emergency/Electronic <input type="checkbox"/> Streamlined
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7608	Administrative Advice: Special Pricing Arrangements apply.
21155	Indication: Familial heterozygous hypercholesterolaemia
	Treatment Phase: Initial treatment
7792	Clinical criteria:
7791	The treatment must be in conjunction with dietary therapy and exercise
	AND
22831	Clinical criteria:
19607	The condition must have been confirmed by genetic testing; or
22832	The condition must have been confirmed by a Dutch Lipid Clinic Network Score of at least 6
	AND
22836	Clinical criteria:
edit 22833	Patient must have an LDL cholesterol level in excess of 3-3 2.6 millimoles per litre in the presence of symptomatic atherosclerotic cardiovascular disease; or
22834	Patient must have an LDL cholesterol level in excess of 5 millimoles per litre
	AND
22840	Clinical criteria:
edit 22837	Patient must have been treated with the maximum recommended <i>or tolerated</i> dose of atorvastatin or rosuvastatin according to the TGA-approved Product Information for at least 3 months in conjunction with dietary therapy and exercise; or
22838	Patient must have developed clinically important product-related adverse events necessitating withdrawal of statin treatment to trials of each of atorvastatin and rosuvastatin; or
22839	Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information
	AND
22842	Clinical criteria:
22841	Patient must have been treated with ezetimibe for at least 3 months in conjunction with dietary therapy and exercise
	AND
22846	Treatment criteria:
22845	Must be treated by a specialist physician
7840	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

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	<p>(ii) Myositis (clinically important creatine kinase elevation, with or without muscle symptoms) demonstrated by results twice the upper limit of normal on a single reading or a rising pattern on consecutive measurements and which is unexplained by other causes; or</p> <p>(iii) Unexplained, persistent elevations of serum transaminases (greater than 3 times the upper limit of normal) during treatment with a statin.</p>
edit 22847	<p>Prescribing Instructions: Symptomatic atherosclerotic cardiovascular disease is defined as:</p> <p>(i) the presence of symptomatic coronary artery disease (<i>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)</i>); or</p> <p>(ii) the presence of symptomatic cerebrovascular disease (<i>prior ischaemic stroke, revascularisation procedure, or transient ischaemic attack associated with 50% or greater stenosis in 1 or more cerebral arteries on imaging</i>); or</p> <p>(iii) the presence of symptomatic peripheral arterial disease (<i>prior acute ischaemic event due to atherosclerosis, prior revascularisation procedure, or symptoms of ischaemia with evidence of significant peripheral artery disease (50% or greater stenosis in 1 or more peripheral arteries on imaging)</i>).</p>
edit 22876	<p>Prescribing Instructions: The qualifying LDL cholesterol level following <i>at least 3 months' treatment with ezetimibe and a statin (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)</i> must be provided at the time of application documented in the patient's medical records and must be no more than 2 months old.</p>
edit 22877	<p>Prescribing Instructions: The physician must attempt to treat the patient with the maximum recommended <i>or tolerated</i> dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily).</p>
22878	<p>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). This retrial should occur after a washout period of at least 1 month, or if the creatine kinase (CK) level is elevated retrial should not occur until CK has returned to normal.</p>
22879	<p>Prescribing Instructions: In the event of a trial of an alternative statin, it is recommended that the patient is started with the minimum dose of statin in conjunction with ezetimibe. The dose of the alternative statin should be increased not more often than every 4 weeks until the maximum tolerated dose has been reached or target LDL-c has been achieved.</p>
edit 22917	<p>Prescribing Instructions: At the time of application, one of the following must be provided <i>documented in the patient's medical records:</i></p> <p>(i) Confirmation that the patient was treated with atorvastatin 80 mg or rosuvastatin 40 mg for 3 months; or</p> <p>(ii) The doses and duration of treatment and adverse events experienced with trials with each of atorvastatin and rosuvastatin; or</p> <p>(iii) Confirmation that the patient is contraindicated to treatment with a statin as defined in the TGA-approved Product Information.</p>
remove 22881 FULL	<p>Prescribing Instructions: The authority application must be made in writing and must include:</p> <p>a) A completed authority prescription form; and</p> <p>b) A completed Familial heterozygous hypercholesterolaemia Initial PBS Authority Application – Supporting Information Form; and</p> <p>c) The date of consultation and the full name of the specialist physician; and</p> <p>d) A copy of the qualifying Dutch Lipid Clinic Network Score or a copy of the result of genetic testing; and</p> <p>e) The result of LDL cholesterol level and one of the following where appropriate: statin treatment details including agent, dose and treatment duration; or details of adverse events to each of atorvastatin and rosuvastatin or contraindication to treatment with a statin as defined in the TGA-approved Product Information.</p>
Insert new	<p>Prescribing Instructions: <i>One of the following must be documented in the patient's medical records:</i></p> <p><i>(i) the qualifying Dutch Lipid Clinic Network Score; or</i></p> <p><i>(ii) the result of genetic testing</i></p>
remove 7753 CAR	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p>

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	Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7004
insert new (1)	Administrative Advice: Authority applications for initial treatment may be made by telephone to the Authority Prescription Applications 24 hour service on free call 1800 888 333 or via the Health Professional Online Services (HPOS) website.

He-FH listing – continuation

- 1.3 Amend the existing continuation treatment restriction in familial heterozygous hypercholesterolaemia as follows:
- 1) Change Authority approval method from telephone/emergency/electronic to streamlined; and
 - 2) Remove concept 7767; and
 - 3) Update retired concept 21261

Restriction Summary 8108 / ToC: 8108: Authority Required

Concept ID:	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	Restriction Level / Method: <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Emergency/Electronic <input checked="" type="checkbox"/> Streamlined [new code]
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7608	Administrative Advice: Special Pricing Arrangements apply.
21155	Indication: Familial heterozygous hypercholesterolaemia
	Treatment Phase: Continuing treatment
remove 21261 R	Clinical criteria:
21260	Patient must have previously received PBS-subsidised treatment with this drug for this condition
insert 11365	Clinical criteria:
11364	Patient must have previously received PBS-subsidised treatment with this drug for this condition.
	AND
7792	Clinical criteria:
7791	The treatment must be in conjunction with dietary therapy and exercise
remove 7767 CAR	Administrative Advice: Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

He-FH grandfather listing

1.4 Amend the following grandfather restriction to:

- 1) allow the patient population that would have qualified for PBS-subsidy had the LDL cholesterol level criteria been 2.6 mmol instead of 3.3 mmol; and
- 2) change the Authority approval method from 'In writing' to 'Telephone/emergency/electronic'

Restriction Summary 8077 / ToC: 8064: Authority Required

Concept ID	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	Restriction Level / Method: <input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Emergency/Electronic <input type="checkbox"/> Streamlined
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7608	Administrative Advice: Special Pricing Arrangements apply.
21155	Indication: Familial heterozygous hypercholesterolaemia
	Treatment Phase: Grandfather treatment
20200	Clinical criteria:
edit 20199	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to 4 November 2018 [1 Month 20XX; insert new listing date here]
	AND
7792	Clinical criteria:
7791	The treatment must be in conjunction with dietary therapy and exercise
	AND
22831	Clinical criteria:
19607	The condition must have been confirmed by genetic testing; or
22832	The condition must have been confirmed by a Dutch Lipid Clinic Network Score of at least 6
	AND
22884	Clinical criteria:
edit 22882	Patient must have had an LDL cholesterol level in excess of 3.3 2.6 millimoles per litre in the presence of symptomatic atherosclerotic cardiovascular disease at the time non-PBS subsidised treatment with this drug for this condition was initiated; or
22883	Patient must have had an LDL cholesterol level in excess of 5 millimoles per litre at the time non-PBS subsidised treatment with this drug for this condition was initiated
	AND
22887	Clinical criteria:
edit 22885	Patient must have been treated with the maximum <i>recommended</i> or tolerated dose of atorvastatin or rosuvastatin according to the TGA-approved Product Information for at least 3 months in conjunction with dietary therapy and exercise prior to initiating non-PBS subsidised treatment with this drug for this condition; or
22886	Patient must have developed clinically important product-related adverse events necessitating withdrawal of statin treatment to trials of each of atorvastatin and rosuvastatin prior to initiating non-PBS subsidised treatment with this drug for this condition; or
22839	Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information
insert	AND
22842	Clinical criteria:
22841	Patient must have been treated with ezetimibe for at least 3 months in conjunction with dietary therapy and exercise

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	AND
22846	Treatment criteria:
22845	Must be treated by a specialist physician
7840	<p>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.</p>
edit 22847	<p>Prescribing Instructions: Symptomatic atherosclerotic cardiovascular disease is defined as: (i) the presence of symptomatic coronary artery disease (<i>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)</i>); or (ii) the presence of symptomatic cerebrovascular disease (<i>prior ischaemic stroke, revascularisation procedure, or transient ischaemic attack associated with 50% or greater stenosis in 1 or more cerebral arteries on imaging</i>); or (iii) the presence of symptomatic peripheral arterial disease (<i>prior acute ischaemic event due to atherosclerosis, prior revascularisation procedure, or symptoms of ischaemia with evidence of significant peripheral artery disease (50% or greater stenosis in 1 or more peripheral arteries on imaging)</i>).</p>
edit 22906	<p>Prescribing Instructions: The qualifying LDL cholesterol level level <i>following at least 3 months' treatment with ezetimibe and a statin (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)</i> must be provided at the time of application <i>documented in the patient's medical records</i> and must have been no more than 2 months old at the time non-PBS subsidised treatment with this drug for this condition was initiated. If the patient has developed a clinically important product-related adverse event, the clinician must confirm at the time of the application that the maximum tolerated dose of atorvastatin or rosuvastatin has been trialled and has resulted in the patient developing a clinically important product-related adverse event resulting in treatment withdrawal.</p>
edit 22878	<p>Prescribing Instructions: If treatment with atorvastatin or rosuvastatin resulted <i>resulted</i> in development of a clinically important product-related adverse event resulting in treatment withdrawal, the patient must <i>have been</i> treated with the alternative statin (atorvastatin or rosuvastatin). This retrial should have occurred <i>retrial should have occurred</i> after a washout period of at least 1 month, or if the creatine kinase (CK) level was elevated <i>was elevated</i> the retrial should not have occurred <i>retrial should not have occurred</i> until CK hasd <i>hasd</i> returned to normal.</p>
edit 22907	<p>Prescribing Instructions: In the event of a trial of an alternative statin, the dose of the alternative statin should <i>have been</i> increased not more often than every 4 weeks until the maximum tolerated dose was been <i>was been</i> reached or target LDL-c hasd <i>hasd</i> been achieved. With the exception of the situation where the patient is contraindicated to treatment with a statin, the doses and duration of treatment and adverse events experienced with trials with each of atorvastatin and rosuvastatin must be <i>documented in the patient's medical records</i> provided at the time of application.</p>
22880	<p>Prescribing Instructions: Contraindication to treatment with a statin is as defined in the TGA-approved Product Information.</p>
remove 22908 FULL	<p>Prescribing Instructions: The authority application must be made in writing and must include: a) A completed authority prescription form; and b) A completed Familial heterozygous hypercholesterolaemia Grandfather PBS Authority Application – Supporting Information Form; and c) The date of consultation and the full name of the specialist physician; and d) A copy of the qualifying Dutch Lipid Clinic Network Score or a copy of the result of genetic testing; and e) The result of LDL cholesterol level and one of the following where appropriate: statin treatment details including agent, dose and treatment duration; or details of adverse events to each of atorvastatin and rosuvastatin or contraindication to treatment with a statin as defined in the TGA-approved Product Information.</p>
Insert new	<p>Prescribing Instructions: <i>One of the following must be documented in the patient's medical records:</i></p>

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	(i) the qualifying Dutch Lipid Clinic Network Score; or (ii) the result of genetic testing
delete 20162 RETIRED	Prescribing Instructions: A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
Insert 23701	Prescribing Instructions: A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the continuing treatment criteria.
remove 7753 CAR	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001
insert New (2)	Administrative Advice: Authority applications for grandfathered treatment may be made by telephone to the Authority Prescription Applications 24 hour service on free call 1800 888 333 or via the Health Professional Online Services (HPOS) website.

Ho-FH listing

- 1.5 Amend existing familial homozygous hypercholesterolaemia restrictions as follows:
- 1) revise LDL-c eligibility threshold from 3.3 mmol/L to 2.6 mmol/L in concept ID: 22909; and
 - 2) clarify that the qualifying LDL cholesterol level must be following 3 months treatment with ezetimibe and a statin in concept ID: 22876; and
 - 3) change ‘...maximum recommended dose of atorvastatin or rosuvastatin’ to ‘...maximum recommended or tolerated dose of atorvastatin or rosuvastatin’ in concept IDs: 22387 & 22877; and
 - 4) change the Authority approval method for the initial restriction from ‘In writing’ to ‘Telephone/Emergency/Electronic’.

Name, restriction, manner of administration, form	Max. Qty (packs)	Max. Qty (units)	No. of repeats	PBS item code	Proprietary name and manufacturer
EVOLUCUMAB, 140 mg/mL injection, 1 mL pen device	3	3	5	10958R	Repatha® Amgen
EVOLUCUMAB, 420 mg/mL injection, 3.5 mL cartridge	1	1	5	11193D	Repatha® Amgen

Restriction Summary 8063 / ToC: 8094: Authority Required

Concept ID	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	Restriction Level / Method: <input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Emergency/Electronic <input type="checkbox"/> Streamlined
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7608	Administrative Advice: Special Pricing Arrangements apply.

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10886	Indication: Familial homozygous hypercholesterolaemia
	Treatment Phase: Initial treatment
7792	Clinical criteria:
7791	The treatment must be in conjunction with dietary therapy and exercise
	AND
19609	Clinical criteria:
19607	The condition must have been confirmed by genetic testing; or
19608	The condition must have been confirmed by a Dutch Lipid Clinic Network Score of at least 7
	AND
22910	Clinical criteria:
edit 22909	Patient must have an LDL cholesterol level in excess of 3.3 2.6 millimoles per litre
	AND
22912	Clinical criteria:
edit 22837	Patient must have been treated with the maximum recommended <i>or tolerated</i> dose of atorvastatin or rosuvastatin according to the TGA-approved Product Information for at least 3 months in conjunction with dietary therapy and exercise; or
22911	Patient must have developed a clinically important product-related adverse event necessitating withdrawal of statin treatment; or
22839	Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information
	AND
22846	Treatment criteria:
22845	Must be treated by a specialist physician
7840	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.
edit 22876	Prescribing Instructions: The qualifying LDL cholesterol level <i>following at least 3 months' treatment with a statin (unless treatment with a statin is contraindicated, or following completion of a statin trial as described in these prescriber instructions in the event of a clinically important adverse event)</i> must be provided documented in the patient's medical records at the time of application and must be no more than 2 months old.
edit 22877	Prescribing Instructions: The physician must attempt to treat the patient with the maximum recommended <i>or tolerated</i> dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily).
edit 22913	Prescribing Instructions: With the exception of the situation where the patient is contraindicated to treatment with a statin, the agent, dose and duration of statin treatment must be provided documented in the patient's medical records at the time of application.
22880	Prescribing Instructions: Contraindication to treatment with a statin is as defined in the TGA-approved Product Information.
remove 22914 FULL	Prescribing Instructions: The authority application must be made in writing and must include: a) A completed authority prescription form; and b) A completed Familial homozygous hypercholesterolaemia Initial PBS Authority Application – Supporting Information Form; and c) The date of consultation and the full name of the specialist physician; and d) A copy of the qualifying Dutch Lipid Clinic Network Score or a copy of the result of genetic testing; and e) The result of LDL cholesterol level and one of the following where appropriate: statin treatment details including agent, dose and treatment duration; or details of adverse event or contraindication to treatment with a statin as defined in the TGA-approved Product Information.

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Insert new	Prescribing Instructions: One of 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
remove 7753 CAR	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7004
insert New (1)	Administrative Advice: Authority applications for initial treatment may be made by telephone to the Authority Prescription Applications 24 hour service on free call 1800 888 333 or via the Health Professional Online Services (HPOS) website.

Ho-FH listing – continuation

1.6 Amend the existing continuation treatment restriction in familial heterozygous hypercholesterolaemia as follows:

- 1) change the Authority approval method from 'Telephone/Emergency/Electronic' to Streamlined; and
- 2) remove complex authority required flag/concept ID 7767

Restriction Summary 8107 / ToC: 6597: Authority Required

Concept ID:	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	Restriction Level / Method: <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Emergency/Electronic <input checked="" type="checkbox"/> Streamlined [new code]
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7608	Administrative Advice: Special Pricing Arrangements apply.
10886	Indication: Familial homozygous hypercholesterolaemia
	Treatment Phase: Continuing treatment
11365	Clinical criteria:
11364	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
7792	Clinical criteria:
7791	The treatment must be in conjunction with dietary therapy and exercise
remove 7767 CAR	Administrative Advice: Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

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Ho-FH grandfather listing

- 1.7 Add the following new grandfather restriction to allow the patient population that would have qualified for PBS-subsidy had the LDL cholesterol level criterion been 2.6 mmol instead of 3.3 mmol:

Restriction Summary [New] / ToC: [New]

Concept ID	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	Restriction Level / Method: <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Emergency/Electronic <input type="checkbox"/> Streamlined
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7608	Administrative Advice: Special Pricing Arrangements apply.
10886	Indication: Familial homozygous hypercholesterolaemia
	Treatment Phase: Grandfather treatment
20200	Clinical criteria:
edit 20199	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to 4 November 2018 [1 Month 20XX; insert new listing date here]
7792	Clinical criteria:
7791	The treatment must be in conjunction with dietary therapy and exercise
	AND
19609	Clinical criteria:
19607	The condition must have been confirmed by genetic testing; or
19608	The condition must have been confirmed by a Dutch Lipid Clinic Network Score of at least 7
	AND
22910	Clinical criteria:
edit 22909	Patient must have an LDL cholesterol level in excess of 3.3 2.6 millimoles per litre
	AND
22912	Clinical criteria:
edit 22837	Patient must have been treated with the maximum recommended <i>or tolerated</i> dose of atorvastatin or rosuvastatin according to the TGA-approved Product Information for at least 3 months in conjunction with dietary therapy and exercise; or
22911	Patient must have developed a clinically important product-related adverse event necessitating withdrawal of statin treatment; or
22839	Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information
	AND
22846	Treatment criteria:
22845	Must be treated by a specialist physician
7840	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.
edit	Prescribing Instructions:

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22906	The qualifying LDL cholesterol level <i>following at least 3 months' treatment with ezetimibe and a statin (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)</i> must be provided <i>documented in the patient's medical records</i> at the time of application and must have been no more than 2 months old at the time non-PBS subsidised treatment with this drug for this condition was initiated. If the patient has developed a clinically important product-related adverse event, the clinician must confirm at the time of the application that the maximum tolerated dose of atorvastatin or rosuvastatin has been trialled and has resulted in the patient developing a clinically important product-related adverse event resulting in treatment withdrawal.
edit 22878	Prescribing Instructions: If treatment with atorvastatin or rosuvastatin resulted in development of a clinically important product-related adverse event resulting in treatment withdrawal, the patient must <i>have been</i> treated with the alternative statin (atorvastatin or rosuvastatin). This retrial should <i>have occurred</i> after a washout period of at least 1 month, or if the creatine kinase (CK) level was elevated retrial should not <i>have occurred</i> until CK has returned to normal.
edit 22907	Prescribing Instructions: In the event of a trial of an alternative statin, the dose of the alternative statin should <i>have been</i> increased not more often than every 4 weeks until the maximum tolerated dose has been reached or target LDL-c has been achieved. With the exception of the situation where the patient is contraindicated to treatment with a statin, the doses and duration of treatment and adverse events experienced with trials with each of atorvastatin and rosuvastatin must be provided <i>documented in the patient's medical records</i> at the time of application.
22880	Prescribing Instructions: Contraindication to treatment with a statin is as defined in the TGA-approved Product Information.
new	Prescribing Instructions: <i>One of the following must be documented in the patient's medical records:</i> <i>(i) the qualifying Dutch Lipid Clinic Network Score; or</i> <i>(ii) the result of genetic testing</i>
23701	Prescribing Instructions: A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the continuing treatment criteria.
New (2)	Administrative Advice: <i>Authority applications for grandfather treatment may be made by telephone to the Authority Prescription Applications 24 hour service on free call 1800 888 333 or via the Health Professional Online Services (HPOS) website.</i>

Alirocumab flow-ons

1.8 *Amend the March 2019 PBAC recommendation for alirocumab as follows (amendments not shown here):*

- 1) *clarify that the qualifying LDL cholesterol level must be following 3 months treatment with ezetimibe and a statin in concept ID: 22876 where used; and*
- 2) *change '...maximum recommended dose of atorvastatin or rosuvastatin' to '...maximum recommended or tolerated dose of atorvastatin or rosuvastatin' in concept IDs: 22387 & 22877 where used; and*
- 3) *change the Authority approval method from 'In writing' to 'Telephone/Emergency/Electronic'.*

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

7 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.

8 Sponsor's Comment

Amgen is pleased that evolocumab will be made available on the PBS for additional Australian patients at high risk of serious cardiovascular events.