

4.05 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

1 Purpose of Application

1.1 The minor resubmission sought an Authority Required listing for treatment of patients with Familial Hypercholesterolaemia (FH) and either symptomatic atherosclerotic cardiovascular disease (ASCVD) or FH with very high LDL-c. The following changes were included:

- a revised economic model for FH with ASCVD and FH with very high LDL-c to incorporate a lag in effect of cardiovascular (CV) mortality and a price reduction of approximately █%
- revised financial estimates incorporating the reduced price offer and removal of the cost offsets from ezetimibe substitution
- a proposal for a risk-share arrangement with a three tier cap
- revised restriction wording with respect to demonstration of statin intolerance, and wording relating to use of evolocumab in combination with other lipid lowering therapy.

2 Background

Registration status

- 2.1 Evolocumab was approved by the TGA on 4 December 2015 for the treatment of:
- Adults with heterozygous Familial Hypercholesterolaemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD):
 - in combination with a statin or statin with other lipid lowering therapies,
 - in combination with other lipid-lowering therapies in patients who are statin-intolerant.
 - Homozygous Familial Hypercholesterolaemia (HoFH)
 - in combination with other lipid lowering therapies in adults and adolescents aged 12 years and over.
- 2.2 The TGA indication notes that the effect of evolocumab on cardiovascular morbidity and mortality has not yet been determined. A TGA application to broaden the

registered indication, on the basis of the results of the FOURIER CV outcomes trial, was lodged in June 2017 and approval was anticipated 31 August 2018.

Previous PBAC consideration

- 2.3 Evolocumab was listed on the PBS on 1 December 2016 for HoFH.
- 2.4 The outstanding matters of concerns from the November 2017 meeting are summarised in the table below.

Table 1: PBAC matters of concern in previous consideration (November 2017)

Matters of concern		How the resubmission addresses it
(para 7.11) The PBAC considered a resubmission for the FH populations should include the following:		
Restriction:	Restriction with more specific definitions of ASCVD and statin intolerance, and clarity that patients are required to be on other lipid lowering therapy/ies to be eligible for evolocumab	<p>No changes were proposed to the definition of ASCVD.</p> <p>The revised restriction includes wording with respect to demonstration of statin intolerance, and wording relating to use of evolocumab in combination with other lipid lowering therapy.</p> <p>These proposed changes are outlined below in Section 3.</p> <p>The PBAC was requested to consider the status of the TGA submission for the monotherapy TGA indication expansion (expected approval in August 2018) and not include the addition of monotherapy to the PBS restriction or include a time limited note if PBS listed prior to TGA approval. The PBAC considered the request to not prohibit monotherapy was reasonable.</p>
Alirocumab comparison	Indirect comparison with alirocumab using the FOURIER trial and ODYSSEY OUTCOMES trial data, if available	Not addressed in this minor resubmission, but an indirect comparison would be presented in a future submission to the PBAC when the ODYSSEY OUTCOMES data is available.
Model	Revised base cases for both the FH with ASCVD and FH with very high LDL-c populations incorporating a time lag for CV mortality benefit of between [redacted] years and a reduced price to achieve comparable ICERs to those presented in this November 2017 submission	<p>Comparable ICERs to those presented in November 2017 with the revised model, which includes:</p> <ul style="list-style-type: none"> - a [redacted] year lag in CV mortality effects - an approximate [redacted]% price reduction for the effective price
Financial estimates	Revised financial implications for the FH population only, including a risk-share arrangement with a cap to account for uncertainty on the size and uptake of the eligible FH population and potential use outside the approved FH population into the non-FH population.	<p>The revised financial estimates incorporate the reduced price offer and remove the cost offsets from ezetimibe substitution.</p> <p>A risk-share arrangement with a three tier cap is proposed. A [redacted]% rebate would apply between Tier 1 and Tier 2. Above Tier 2, a [redacted]% rebate is proposed. No detail of the rationale for the selected Tier 2 values has been provided. The estimates are approximately [redacted]% higher than Tier 1.</p>
(para 7.12) Non-FH with ASCVD population: The PBAC rejected this component of the submission. The PBAC considered the population was inadequately defined. The PBAC advised further modelling could be used to determine the qualifying LDL-c level for the non-FH population with ASCVD, and the proposed PBS restriction would require more specific definitions of ASCVD and statin intolerance.		Not addressed in this minor resubmission.

Source: Compiled by the Secretariat. Paragraph references refer to the November 2017 evolocumab minutes.

For more detail on PBAC’s view, see section 5 PBAC outcome.

3 Requested listing

3.1 This resubmission does not include the non-FH ASCVD population, which was the component of the November 2017 submission rejected by the PBAC. The changes to the proposed listing for the FH populations are highlighted below in grey; these changes relate to the criteria defining statin intolerance.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Published (Effective) Dispensed price for maximum quantity	Proprietary Name and Manufacturer
EVOLOCUMAB				
140 mg injection, 1 mL injection device	2	5	\$ [redacted] ^a (\$ [redacted] ^b)	Repatha Sureclick®
420 mg injection, 3.5 mL injection device	1	5	\$ [redacted] ^a (\$ [redacted] ^b)	Repatha Automated Mini-Doser® Amgen

a. Prices updated to reflect current AHI and dispensing fees.

b. Proposed effective price based on calculation consistent with that used to derive current effective prices and updated to reflect proposed [redacted]% rebate (previously [redacted]%).

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
Condition:	Familial hypercholesterolaemia
PBS Indication:	Familial hypercholesterolaemia
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment phase	Initial treatment

<p>Clinical criteria:</p>	<p>The treatment must be in conjunction with dietary therapy and exercise</p> <p>AND</p> <p>The condition must have been confirmed by genetic testing; OR</p> <p>The condition must have been confirmed by a Dutch Lipid Clinic Network Score of at least 6</p> <p>AND</p> <p>Patient must have an LDL cholesterol level in excess of 5 millimoles per litre, or 3.3 millimoles per litre in the presence of symptomatic atherosclerotic cardiovascular disease, after at least 3 months of treatment at a maximum tolerated dose of an HMG CoA reductase inhibitor (statin), in conjunction with dietary therapy and exercise; OR</p> <p>Patient must have an LDL cholesterol level in excess of 5 millimoles per litre, or 3.3 millimoles per litre in the presence of symptomatic atherosclerotic cardiovascular disease, after having developed a clinically important product-related adverse event after a trial of treatment with at least 2 different HMG CoA reductase inhibitors (statins) necessitating a withdrawal of statin treatment; OR</p> <p>Patient must have an LDL cholesterol level in excess of 5 millimoles per litre, or 3.3 millimoles per litre in the presence of symptomatic atherosclerotic cardiovascular disease, and must be one in whom treatment with an HMG CoA reductase inhibitor (statin) is contraindicated.</p>
<p>Treatment criteria:</p>	<p>Must be treated by a consultant physician or in consultation with a consultant physician.</p> <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>The date of the consultation with a consultant physician must be no more than 6 months prior to the application for a PBS authority. The full name of the consultant physician consulted and the date of consultation are to be provided at the time of application.</p> <p>The qualifying LDL cholesterol level must be provided at the time of application and must be no more than 2 months old. For patients not on the highest possible statin dose (i.e. 80 mg atorvastatin or 40 mg rosuvastatin), clinicians must confirm that a higher dose statin has been trialled and not tolerated. For patients intolerant of statin therapy, the agents, doses and duration of treatment and adverse events experienced with at least 2 statins must be provided at the time of application. For patients contraindicated to statin therapy, details of the contraindication must be provided at the time of the application.</p> <p>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 hypercholesterolaemia Initial PBS Authority Application - Supporting Information Form; and</p> <p>c) The date of consultation and the full name of the consultant 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 event or contraindication to treatment with a statin as defined in the TGA-approved Product Information.</p>

	f) Where the qualifying LDL cholesterol level is less than or equal to 5 mmol/L, details of the diagnosis of symptomatic atherosclerotic cardiovascular disease must be provided.
Notes	<p>Special Pricing Arrangements apply</p> <p>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</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>

- 3.2 In November 2017, the PBAC considered further treatment criteria to define statin intolerance was required, such as a requirement for rechallenging after a treatment break with a lower dose or alternative statin, as suggested by a number of reviews and guidelines (Public Summary Document, paragraph 7.3).
- 3.3 The PBAC Secretariat suggested that should the proposed change to the maximum quantity for the 140 mg injection from 3 to 2 be accepted, a note may be included in the Prescriber Instructions of the restriction which describes when the maximum quantity may be increased for the homozygous FH patients (i.e. where the dose increases from 420 mg monthly to fortnightly). Alternatively, separate PBS listings for homozygous and heterozygous familial hypercholesterolaemia may be considered more appropriate. The pre-PBAC response stated that the sponsor does not believe separate listings for both the homozygous and heterozygous population are needed.
- 3.4 The proposed PBS listing would allow monotherapy with evolocumab in patients who are intolerant/contraindicated to statins and this use is currently outside the approved TGA indication. The resubmission stated that following recent FDA approval, TGA approval for monotherapy with evolocumab is anticipated in August 2018. The sponsor requested the PBAC give consideration to the status of the TGA submission for the inclusion of monotherapy in the product information, and consider recommending a time-limited addition of monotherapy to the PBS restriction (if the TGA outcome is pending), or no addition (if the TGA outcome is successful). The PBAC considered this was reasonable, however it was noted that the TGA indication allows combination with non-statin lipid lowering therapies such as ezetimibe. If a patient is statin intolerant, the PBAC considered it appropriate to encourage concomitant use of ezetimibe to maximise lowering of LDL-c, although it was recognised that there is a limited evidence base for this.

For more detail on PBAC's view, see section 5 PBAC outcome.

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.

Clinical trials

4.3 As a minor submission, no clinical trials were presented in the submission.

Economic analysis

4.4 In the major submission considered by PBAC in November 2017, a stepped economic evaluation of evolocumab was presented for the treatment of:

- FH with ASCVD, with ICERs of \$15,000 - \$45,000 per QALY gained vs ezetimibe and \$15,000 - \$45,000 vs placebo
- FH with very high LDL-c levels, with ICERs of \$15,000 - \$45,000 per QALY gained vs ezetimibe and \$15,000 – \$45,000 vs placebo

4.5 The pre-PBAC response in November 2017 provided sensitivity analyses incorporating a [REDACTED] year time lag in CV mortality benefit for the FH population with ASCVD, with resultant ICERs of \$15,000 – \$45,000 and \$15,000 – \$45,000 per QALY gained, respectively, up from \$15,000/QALY - \$45,000/QALY in the base case, in the comparison with ezetimibe. It was noted the pre-PBAC response introduced the time lag as a switch that uses placebo CV mortality rates for the first two years then switches to evolocumab/ezetimibe mortality for subsequent years. However, slightly different rates of MI and stroke are used in the first two years (which appears to be due to the interaction with increasing odds of death with time in model) which results in anomalies in non-fatal events in active treatment arms. This was considered unlikely to have a substantial impact on the revised ICERs.

4.6 In November 2017, the PBAC considered the mortality benefit modelled in those sensitivity analyses remains optimistic with the [REDACTED]-year time lags, noting that only a small number of statin trials, which have an early treatment effect, showed mortality benefit at two years. The Committee further stated a resubmission should include revised base cases for both the FH with ASCVD and FH with very high LDL-c populations incorporating a time lag for CV mortality benefit of between [REDACTED] [REDACTED] years and a reduced price to achieve comparable ICERs to those presented in this November 2017 submission. (Public Summary Document, paragraphs 7.9 and 7.11).

4.7 The revised model in this minor resubmission includes:

- a [REDACTED] year lag in CV mortality effects

- an approximately [REDACTED]% price reduction for the effective price.

No other changes to the model submitted with the pre-PBAC response in November 2017 were made.

4.8 The revised price proposal with a [REDACTED] year lag in the CV mortality benefit maintains ICERs comparable to those in the November 2017 submission:

- FH with ASCVD, with ICERs of \$15,000 – 45,000 per QALY gained vs ezetimibe and \$15,000 – 45,000 vs placebo
- FH with very high LDL-c levels, with ICERs of \$15,000 – 45,000 per QALY gained vs ezetimibe and \$15,000 – 45,000 vs placebo.

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

4.9 The estimated drug cost for evolocumab per patient per year was \$ [REDACTED] (based on [REDACTED] scripts using the effective DPMQ \$ [REDACTED] for the 140 mg fortnightly injection).

4.10 In November 2017, the estimated drug cost for evolocumab per patient per year was \$ [REDACTED] (based on [REDACTED] scripts using the effective DPMQ \$ [REDACTED] for the 140 mg fortnightly injection).

4.11 The estimated drug cost for ezetimibe per patient per year was \$ [REDACTED] (based on [REDACTED] scripts, using the current DPMQ \$66.84 for ezetimibe 10 mg tablets).

Estimated PBS usage & financial implications

4.12 The minor resubmission estimated a net effective cost to the PBS of \$30 - \$60 million in year 6 of listing, with a total net effective cost to the PBS of more than \$100 million over the first 6 years of listing. This is summarised in the table below as well as the expected patient/prescription numbers.

4.13 These estimates are reduced from \$30 - \$60 million in year 6, and a total net effective cost of more than \$100 million, across FH populations only, in the November 2017 submission. The revised financial estimates incorporated the reduced price offer and removed the cost offsets from ezetimibe substitution, as advised by the DUSC for the November 2017 submission.

Table 2: Estimated utilisation and cost to the PBS of evolocumab in the first six years of listing (effective price less patient copayments)

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Year 6 (2023)
Familial hypercholesterolaemia (FH) with atherosclerotic disease and FH with very high LDL-c						
Treated patients						
Estimated 140 mg scripts						
Estimated 420 mg scripts						
Total cost PBS/RPBS (effective price)	\$	\$	\$	\$	\$	\$
Net cost PBS/RPBS (effective price less co- payments)	\$	\$	\$	\$	\$	\$

Source: summarised from Table 4 of the minor resubmission, p3.

- 4.14 The assumption for FH prevalence of 1:353 is consistent with the DUSC’s advice from November 2017. However DUSC considered that the FH prevalence should be applied to the population aged above 25 years (DUSC Advice November 2017) whereas the resubmission has applied the prevalence rate to the whole Australian population. The pre-PBAC response maintained that evolocumab is indicated in adults and adolescents aged 12 years and over with homozygous FH, and only in adults with heterozygous FH. Given its efficacy in this population, and that FH is also an autosomal inherited disorder present from birth, the sponsor stated that applying prevalence to solely the population aged above 25 would exclude some patients within the eligible population. The PBAC noted that including the whole Australian population when estimating the eligible population increased the prevalent pool of patients from 48,010 people (population aged above 25 years, consistent with the AusDiab study) to 71,392.
- 4.15 As for the prior submission, detection rates (35% in 2018 rising to 75% in 2023) are applied to the whole prevalent population with FH. This ignores the DUSC’s advice that a proportion of patients with symptomatic FH disease should be removed before applying the detection rates as they would already be diagnosed. The pre-PBAC response argued that the diagnosis of FH cannot be assumed despite symptomatic disease on the basis that the diagnosis rate of FH with or without ASCVD has not changed and is currently low. It also stated that diagnostic tests can be complicated and costly, and may not have been routinely performed in the past.
- 4.16 The resubmission based its estimate of the proportion of FH patients with ASCVD (40%) on the AusDiab study. DUSC previously considered that this was an appropriate source for this assumption.
- 4.17 The financial estimates are highly sensitive to the assumption for the proportion of patients with LDL-c above the eligibility threshold. These are unchanged from the prior submission and no further justification is provided in the resubmission for their

selection. DUSC considered that the assumptions were highly uncertain but noted there was a lack of sources to inform them.

- 4.18 The uptake rates for FH ASCVD and FH primary prevention are unchanged from the prior submission. DUSC considered that these assumptions were overestimated noting the uptake of other medicines given by subcutaneous injection were lower. The pre-PBAC response provided reasoning for the potential estimated uptake of evolocumab and stated that the main contributing factor may be the characteristics of evolocumab therapy relative to alternatives, not that it is an injectable therapy.

Financial management – risk sharing arrangements

- 4.19 The current listing of evolocumab is subject to a special pricing arrangement (█% rebates on government expenditure). The minor resubmission proposed a revision of the special pricing arrangement to include a further discount for the expanded listing (█% rebate on government expenditure; this is increased from █% in the November 2017 submission).
- 4.20 In November 2017, the PBAC considered a new risk-share arrangement would need to incorporate a cap on financial estimates for PCSK9 inhibitors to account for potential use in the non-FH population (Public Summary Document, paragraph 7.10).
- 4.21 In this minor resubmission, the sponsor has proposed a tiered financial cap arrangement to address uncertainty in the extent of use. The Tiers are outlined in the table below. The Tier 1 caps are based on the resubmission estimates of the number of eligible patients forecast to receive evolocumab in the base case. A █% rebate would apply between Tier 1 and Tier 2. Above Tier 2, a █% rebate was proposed.

Table 3: Proposed tiered financial caps – Commonwealth Payment

DPMQ copayment	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Net cost of evolocumab to the PBS/RPBS (BASE)	\$█	\$█	\$█	\$█	\$█	\$█
TIER 1 Same as above	\$█	\$█	\$█	\$█	\$█	\$█
	█% repayment for Commonwealth payment between Tier 1 and 2					
TIER 2	\$█	\$█	\$█	\$█	\$█	\$█
	█% repayment for Commonwealth Payment beyond Tier 2					

Source: Table 6 of the minor resubmission, p7.

- 4.22 No detail of the rationale for the selected Tier 2 values has been provided. The estimates are approximately ■■■% higher than Tier 1. The pre-PBAC response stated that an approximate ■■■% increase was included to account for the uncertainty of evolocumab use in the eligible FH population as well as the fact people prescribed evolocumab will derive benefit. The PBAC noted this response did not justify the choice of ■■■% as the estimate of that uncertainty.

For more detail on PBAC's view, see section 5 PBAC Outcome.

5 PBAC Outcome

- 5.1 The PBAC recommended an Authority Required listing of evolocumab for the treatment of patients with familial hypercholesterolaemia (FH) based on the revised economic model and the reduced price proposed, which addressed outstanding issues raised by the PBAC from the November 2017 submission. The PBAC recommended that the initial restriction be an Authority Required (in writing) and the continuing restriction be an Authority Required (telephone) restriction. The PBAC accepted that both the heterozygous and homozygous FH populations are high risk, and that the use of evolocumab could be extended to include the heterozygous population as it would be an effective and safe therapy following failed treatment with statins and ezetimibe. The PBAC acknowledged that the financial risk of potential use outside of the approved restriction can be minimised with the hard cap in proposed risk-share arrangement.
- 5.2 The PBAC considered the proposed amendments to the definition of statin intolerance were helpful. However, the PBAC suggested the revised wording should also include a period of time in which a statin should be re-challenged before the commencement of evolocumab (at least one week apart). The PBAC advised that a trial of ezetimibe should also be included in the restriction.
- 5.3 The PBAC considered a single PBS listing for FH would be appropriate and agreed with the Secretariat's proposal to include increased maximum quantities in the Prescriber Instructions for the homozygous population, as appropriate.
- 5.4 The PBAC noted the sponsor's request to consider the status of the TGA submission to allow monotherapy with evolocumab in patients who are intolerant/contraindicated to statins. The PBAC considered that while continued use of statin and/or ezetimibe should be encouraged, no additional wording to the proposed restriction preventing use of evolocumab as monotherapy was required.
- 5.5 The PBAC recalled from November 2017 that it had considered the clinical claims of superior effectiveness and similar safety to both ezetimibe (based on the lipid trials) and placebo (based on the FOURIER trial) were reasonable.
- 5.6 The PBAC considered the revised economic model and the price adjustment to reflect the delayed CV mortality benefit were acceptable for the heterozygous FH

population. The PBAC noted that the resultant ICERs were comparable to those considered in the November 2017 submission.

- 5.7 The PBAC noted the revised financial estimates appropriately removed cost-offsets for ezetimibe use and incorporated the revised effective price. However, the PBAC noted a number of other issues raised by DUSC in November 2017 were not resolved and considered this contributes to uncertainty in estimating the eligible patient population and uptake. The PBAC noted the sponsor's proposal for an RSA with a tiered cap to account for uncertainty in the size and uptake of the eligible FH population, and potential use outside the approved FH population. The PBAC raised concerns regarding the proposed figures and [REDACTED]% rebate for the Tier 2 cap which were somewhat arbitrary and requires further revision. The PBAC also noted the estimated expenditure in this minor resubmission was for the heterozygous FH population only; the PBAC considered that the RSA would need to encompass the homozygous FH population as well and the hard cap ([REDACTED]% rebate) was essential to containing the risk of use beyond the PBS eligible population.
- 5.8 Evolocumab is currently not included for prescribing by nurse practitioners given that it is the first drug in this class.
- 5.9 Evolocumab should not be exempt from the Early Supply Rule, as it applies to the current PBS listing for evolocumab.
- 5.10 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

Amend existing listing: *to be finalised*.

7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

8 Sponsor's Comment

Amgen is pleased that the PBAC has recommended evolocumab for all FH patients who are at very high CV risk and require access to effective therapy to achieve reductions in LDL-C to target levels.