Evolocumab for heterozygous familial hypercholesterolaemia: predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

June 2021

Abstract

Purpose

To compare the predicted and actual utilisation of evolocumab for heterozygous familial hypercholesterolaemia (HeFH) in the first 24 months of PBS listing. Evolocumab was PBS listed for this indication on 1 November 2018.

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

Evolocumab was first listed on the PBS on 1 December 2016.

Data Source / methodology

The analyses used data from the PBS supplied prescriptions and authority approvals databases, extracted from 1 December 2016 to 31 March 2021.

Key Findings

- The actual number of patients treated with evolocumab for familial hypercholesterolaemia in the first two years of listing was lower than expected.
- In 2020, 2,693 patients were supplied at least one prescription for familial hypercholesterolaemia and, of these, 923 patients were supplied their first PBS-subsidised evolocumab prescription for this indication.
- The total number of prescriptions supplied for evolocumab for familial hypercholesterolaemia was lower than predicted.
- Evolocumab is often supplied as a dose of 280 mg or 420 mg as quantities of 2 or 3, 140 mg/mL pen devices. In 2020, the majority of evolocumab prescriptions supplied for familial hypercholesterolaemia were for the 140 mg/mL pen device (17,181 prescriptions; 88%) with a total quantity of 43,675 services; 95%.

Purpose of analysis

To compare the predicted and actual utilisation of evolocumab for heterozygous familial hypercholesterolaemia (HeFH) in the first 24 months of PBS listing. Evolocumab was PBS listed for this indication on 1 November 2018.

Background

Clinical situation

Familial hypercholesterolaemia (FH) is a dominantly inherited disorder present from birth that markedly elevates plasma low-density lipoprotein (LDL) cholesterol and causes premature coronary heart disease. Detailed information on FH is available online from the Familial hypercholesterolaemia Australasia Network.[1]

Pharmacology

Evolocumab is a human monoclonal antibody that binds to proprotein convertase subtilisin/kexin type 9 (PCSK9) and inhibits circulating PCSK9 from binding to the LDL receptor on the liver cell surface, thus preventing PCSK9-mediated LDL receptor degradation. Increasing liver LDL receptor levels results in associated reductions in serum LDL cholesterol.[2]

Therapeutic Goods Administration (TGA) approved indications

Evolocumab is indicated as an adjunct to diet and exercise in:

Prevention of Cardiovascular Events

Evolocumab is indicated 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.

Primary Hypercholesterolaemia

Evolocumab is indicated in adults with primary hypercholesterolaemia (including heterozygous familial hypercholesterolaemia and non-familial hypercholesterolaemia) to reduce low-density lipoprotein cholesterol (LDL-C):

- 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.

Homozygous Familial Hypercholesterolaemia

Evolocumab is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid lowering therapies.

Dosage and administration

Evolocumab is administered by subcutaneous administration.

Table 1: Dosage and administration of evolocumab

Indication	Recommended Dosage and Frequency	Method of Administration
Primary Hypercholesterolaemia and Prevention of Cardiovascular Events	140 mg every 2 weeks	One single-use pre-filled pen
	420 mg once monthly	One single-use automated mini-doser (AMD) with 3.5 mL pre-filled cartridge or Three single-use pre-filled pens administered consecutively within 30 minutes
Homozygous Familial Hypercholesterolaemia	Initial dose is 420 mg once monthly. The dose can be increased to 420 mg every 2 weeks if a clinical meaningful response is not achieved in 12 weeks. Patients on apheresis may initiate treatment with 420 mg every 2 weeks to correspond with apheresis schedule.	One single-use automated mini-doser (AMD) with 3.5 mL pre-filled cartridge or Three single-use pre-filled pens administered consecutively within 30 minutes

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from the TGA (Product Information) and the TGA (Consumer Medicines Information).

PBS listing details (as at March 2021)

Table 2: PBS listing of evolocumab for familial heterozygous hypercholesterolaemia

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
11484K	evolocumab 140 mg/mL injection, 1 mL pen device	2	5	$497.82	Repatha, Amgen Australia Pty Limited
11485L	evolocumab 420 mg/3.5 mL injection, 3.5 mL cartridge	1	5	$539.12	
11985T	evolocumab 140 mg/mL injection, 1 mL pen device	2	5	$497.82	
11986W	evolocumab 420 mg/3.5 mL injection, 3.5 mL cartridge	1	5	$539.12	

Source: the PBS website.

Restriction

Treatment Phase: Initial treatment

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 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 dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily) according to the TGA-approved Product Information or the maximum tolerated dose of atorvastatin or rosuvastatin for at least 12 consecutive weeks in conjunction with dietary therapy and exercise; OR
- Patient must have developed clinically important product-related adverse events necessitating withdrawal of statin treatment to trials of each of atorvastatin and rosuvastatin; OR
- Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information,

AND

- Patient must have been treated with ezetimibe for at least 12 consecutive weeks in conjunction with a statin (if tolerated), dietary therapy and exercise.

Treatment criteria:

Must be treated by a specialist physician.

For definitions of symptomatic atherosclerotic cardiovascular disease, clinically important product-related adverse events and for details of the current PBS listing refer to the PBS website.

Date of listing on PBS

Evolocumab was first PBS listed 1 December 2016.

Changes to listing

Table 3: Changes to the PBS listing of evolocumab

Change	Date
Listed for the treatment of homozygous familial hypercholesterolaemia as Authority Required listings	1 December 2016
Evolocumab 420 mg/3.5 mL injection, 3.5 mL cartridge was PBS listed	1 November 2017
Listing for grandfathered familial homozygous patients deleted	1 February 2018
Listed for the treatment of heterozygous familial hypercholesterolaemia as Authority Required listings under new PBS item codes	1 November 2018
Listed for the treatment of non-familial hypercholesterolaemia under the same PBS item codes as heterozygous familial hypercholesterolaemia	1 May 2020
Listings for continuing treatment changed from Authority Required to Authority Required (Streamlined)	1 May 2020

Current PBS listing details are available from the PBS website.

Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

The PBAC has considered nine submissions for evolocumab since 2015. Out of these submissions, five submissions were for HeFH. Evolocumab submissions for HeFH are outlined in this section. A more detailed summary of all the evolocumab submissions can be found in Appendix A.

March 2015 PBAC Meeting

The submission sought to open a dialogue regarding the potential future listing of evolocumab on the PBS for the treatment of hypercholesterolaemia.

The submission was considered by DUSC. DUSC considered the main issues were:

- The market share approach, based on ezetimibe utilisation, underestimated the population eligible for evolocumab.
- Changing clinical practice, including increased assessment of cardiovascular risk or more widespread treatment to target cholesterol levels, could result in many more patients being treated with evolocumab. Given the high prevalence of dyslipidaemia and the proposed price of evolocumab, small changes in practice could have a large budget impact.
- Significant potential for use beyond the restriction by patients who are not achieving target cholesterol levels, but who would not qualify for evolocumab treatment under the proposed restriction.

The PBAC rejected the request to list evolocumab for the treatment of hypercholesterolaemia on the basis of unestablished clinical place in therapy and the uncertainty surrounding its use in clinical practice.

For further details refer to the Public Summary Document from the March 2015 PBAC meeting.

March 2016 PBAC Meeting

The resubmission requested a Section 85 Authority Required PBS listing for evolocumab for the treatment of familial hypercholesterolaemia. This resubmission was not considered by DUSC.

The PBAC recommended the Section 85 Authority Required listing of evolocumab for homozygous familial hypercholesterolaemia (but not the broader heterozygous familial hypercholesterolaemia population). In making this recommendation, the PBAC considered that the homozygous FH population represent a small, definable, patient group, in whom there is a high level of clinical need.

The PBAC considered that the submission's estimates of usage in the homozygous FH population were more reliable than the estimates for the heterozygous FH population, as there are likely to be less undiagnosed homozygous patients. The PBAC recommended a risk-sharing arrangement (RSA) that should include a cap based on the number of patients treated.

For further details refer to the Public Summary Document from the March 2016 PBAC meeting.

November 2017 PBAC Meeting

The resubmission requested an extension of the current Section 85 (Authority Required) listing for evolocumab to include the treatment of heterozygous familial hypercholesterolaemia (patients with atherosclerotic disease or very high LDL-c levels). This resubmission was considered by DUSC. The resubmission used epidemiological (FH with ASCVD, FH with very high LDL-c) and market share (non-FH with ASCVD) approaches to estimate the utilisation/financial implications associated with the PBS listing of evolocumab.

The PBAC deferred making a recommendation to extend the PBS listing of evolocumab for patients with familial hypercholesterolaemia in order to address the residual uncertainty with the economic model following revisions provided in the pre-PBAC response. The PBAC did not recommend the listing of evolocumab for patients with non-familial hypercholesterolaemia with atherosclerotic disease on the basis of a high incremental cost effectiveness ratio and high and uncertain patient population numbers.

For further details refer to the Public Summary Document from the November 2017 PBAC meeting.

March 2018 PBAC Meeting

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 PBAC recommended extending the PBS listing for evolocumab for patients with Familial Hypercholesterolaemia to include patients with heterozygous FH, under certain conditions. 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 considered that the revised economic model, reduced price and other arrangements proposed in the resubmission addressed the outstanding issues raised by the PBAC from the November 2017 submission.

For further details refer to the Public Summary Document from the March 2018 PBAC meeting.

November 2019 PBAC Meeting

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.

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.

For further details refer to the Public Summary Document from the November 2019 PBAC meeting.

November 2020 PBAC Meeting

The minor submission requested an amendment to the Authority Required listings of evolocumab for all indications to allow general practitioners (GPs) to initiate treatment, but only after having consulted a specialist.

The PBAC did not recommend an amendment to the Authority Required listings of evolocumab for all indications to allow GPs to initiate treatment after having consulted a specialist. The PBAC advised that "Must be treated by a specialist physician" for initiation of treatment should remain for all indications, consistent with its previous advice.

For further details refer to the Public Summary Document from the November 2020 PBAC meeting.

Medical Services Advisory Committee (MSAC) consideration

In March 2019, the MSAC considered an application received from the Royal College of Pathologists of Australasia (RCPA) for diagnostic genetic testing for heritable mutations predisposing to familial hypercholesterolaemia in clinically affected individuals, and for predictive genetic testing (or "cascade testing") of the family members of those affected individuals who are shown to have such a mutation.

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported Medicare Benefits Schedule (MBS) listing of genetic testing for heritable mutations associated with FH in affected individuals meeting defined eligibility criteria, and targeted cascade testing in first and second-degree relatives of those affected individuals with a confirmed genetic diagnosis.

MSAC queried whether the PBS criteria would lead to leakage for an MBS listing, but noted that the Dutch Lipid Clinic Network Score for identifying affected individuals in the proposed MBS item descriptor (at least 6) is similar to the Score used in the alternative option for confirming FH in the PBS restriction for evolocumab (at least 6 for HeFH, and at least 7 for HoFH). In addition, the PBS listing for HoFH patients did not appear to have resulted in large increases in genetic testing, although the listing for HeFH patients was too recent for any data to yet be available. MSAC noted that the pool of HeFH patients is much larger than for HoFH patients.

MSAC queried the criteria for testing in the proposed MBS item descriptor, noting that it differed in some respects from the PBS listing for evolocumab. However, MSAC accepted that these criteria do not have to match. Therefore, MSAC accepted the following criteria for testing of affected individuals who do not have a previously identified FH mutation, but have one or more of the following:

- a Dutch Lipid Clinic Network Score (DLCNS) of at least 6
- a low-density lipoprotein (LDL) cholesterol level of at least 6.5 mmol/L in the absence of secondary causes

- an LDL cholesterol level between 5.0 and 6.5 mmol/L with signs of premature/accelerated atherogenesis.

For further details refer to the MSAC Public Summary Document.

Previous reviews by the DUSC

Evolocumab for familial homozygous hypercholesterolaemia was considered by DUSC at its October 2019 meeting. The number of patients treated with evolocumab in the first two years of listing was higher than expected. DUSC noted to qualify for treatment under HoFH item codes, the condition must have been confirmed by genetic testing or by a DLCNS of at least 7. DUSC considered that as the DLCNS was used by the majority of prescribers to confirm the condition, the actual number of treated patients most likely included both HoFH and HeFH patients.

For details of the DUSC consideration of evolocumab refer to the Public Release Document from the October 2019 DUSC meeting.

Methods

PBS prescription data for evolocumab was extracted from the PBS data maintained by the Department of Health, processed by Services Australia. Data were extracted for dates of supply up to and including 31 March 2021. These prescription data were used to analyse overall use, the age and sex of patients, the supplied dose and time to resupply of evolocumab.

Authorities data were extracted from the Authorities database, and matched to the prescription data to determine the type of hypercholesterolaemia the prescription was intended to treat. Where a streamlined code for hypercholesterolaemia was recorded, this was used in preference to the Authority code.

Consistency of utilisation by indication was investigated, including indication by item code and restriction code for 2020, and the sequence of indication for each patient. Sequence of indication ignored prescriptions with an unknown indication, and assigned the patient 'Unknown' if none of the prescriptions supplied to that patient included an indication. In some analyses a patient's main indication was used. Main indication was determined by the indication recorded on a majority of the patient's prescriptions. If two indications were recorded the same number of times, the patient's main indication was determined by the indication recorded on their initial prescription.

Number of treatments was analysed for patients who had their first initiation to evolocumab in 2019, the number of prescriptions each patient was supplied in the following year was counted.

Treatment duration was analysed using the Kaplan-Meier method. A patient was censored if they were supplied a prescription within three times the median time to resupply prior to 31 March 2021 (i.e. 3×33 days).

As this analysis uses date of supply prescription data, there may be small differences compared with publicly available Medicare date of processing data.[1]

Results

Analysis of drug utilisation

Consistency of utilisation by indication

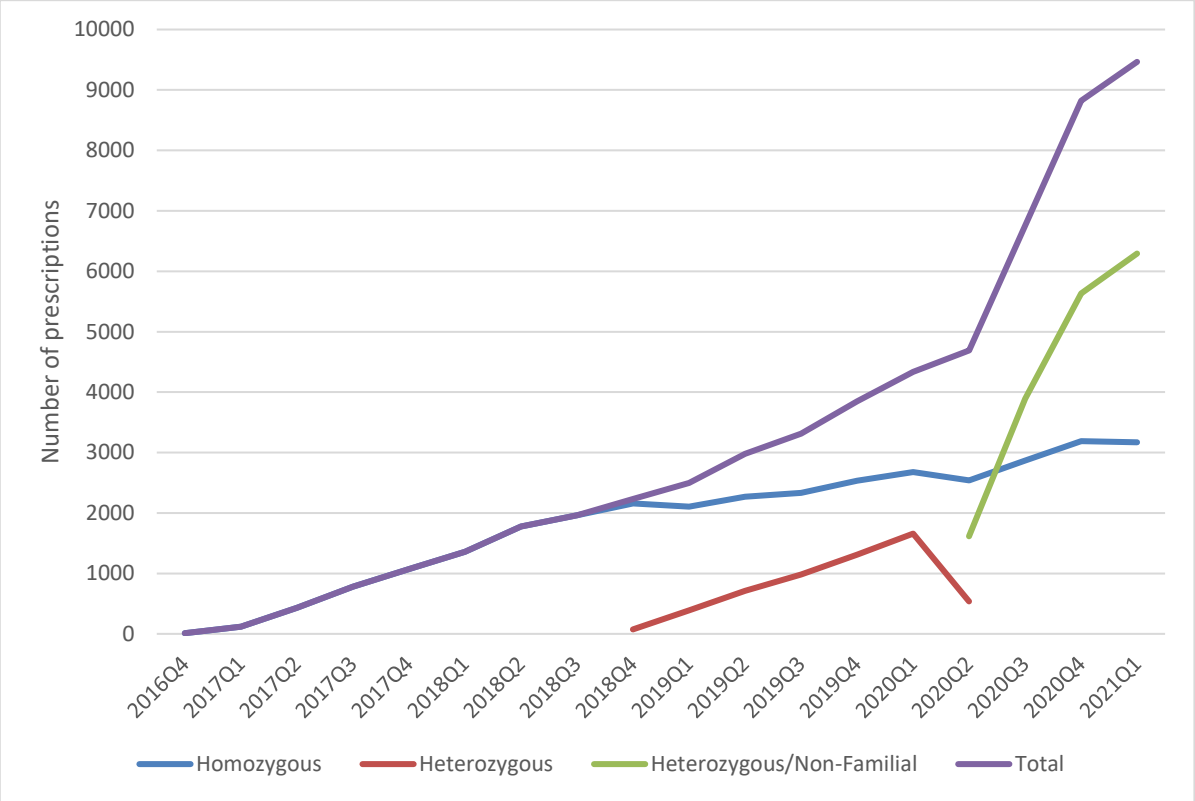

Figure 1: Prescriptions by indication determined by item code

The graph of prescriptions by item code shows that there was an increase in the number of supplied prescriptions when the non-familial listing was added to the heterozygous listing, as the slope of the heterozygous/non-familial line is steeper than the heterozygous.

[1] PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>.

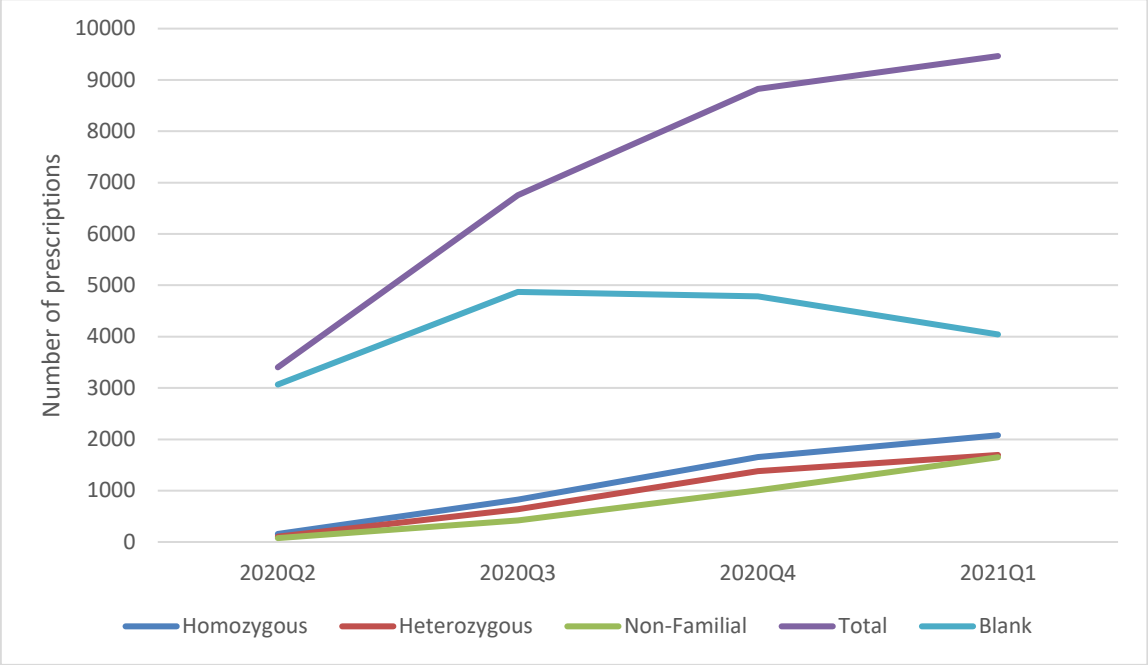

Figure 2: Prescriptions by indication determined by streamlined code

Note: Only includes item codes with Streamlined Authority listings, since Streamlined items were listed on 1 May 2020.

Streamlined listings were added to the PBS on 1 May 2020, when the listings for continuing treatment changed from Authority Required to Authority Required (Streamlined). The non-familial listings were added to the PBS at the same time. Figure 2 shows a large number of these prescriptions do not have a recorded streamlined code, however some of these may have been approved through as Authority Required prescriptions, for example to approve an increased quantity.

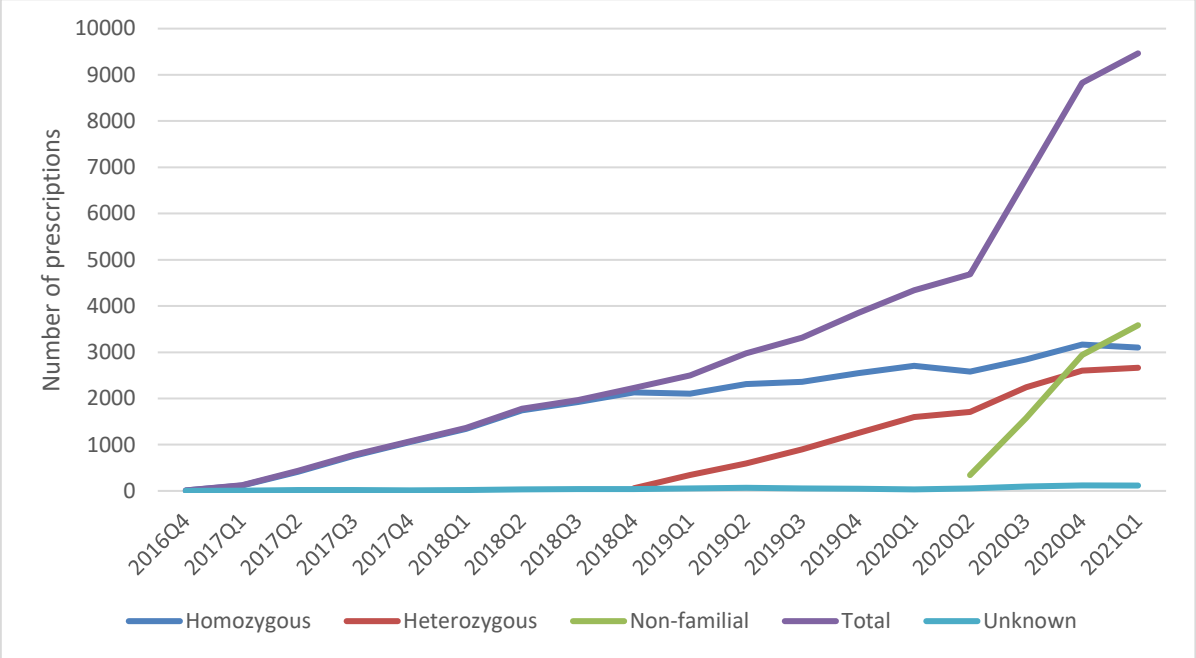

Figure 3: Prescriptions by indication determined by authority or streamlined code

Figure 3 shows that when Authority codes and streamlined codes are used to determine indication, the number of prescriptions with an unknown indications is much smaller.

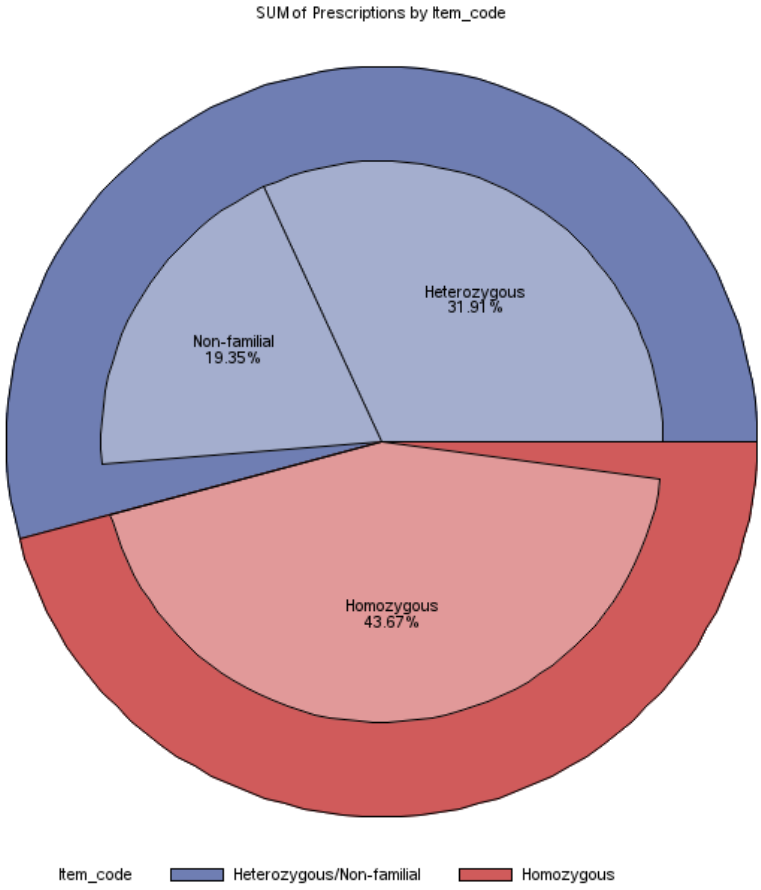

Figure 4: Proportion of prescriptions by indication based on item code and restriction code for 2020

Figure 4 above shows the indication of the item code in the outer circle, and the indication of the restriction code in the inner circle. The number of unknowns or mismatched codes, i.e. a restriction code for homozygous hypercholesterolaemia against an item code for heterozygous hypercholesterolaemia, are represented by the incomplete inner circles, however the numbers of these were too small to be shown.

Table 4: Indication sequence by authority or streamlined code

Indication sequence	Count patients	Percent of total
Homozygous	1,462	33%
Non-familial	1,227	27%
Heterozygous	841	19%
Homozygous>Heterozygous	146	3%
Heterozygous>Non-familial	135	3%
Heterozygous>Homozygous	116	3%
Non-familial>Heterozygous	89	2%
Homozygous>Non-familial	83	2%
Non-familial>Homozygous	67	1%
Homozygous>Heterozygous>Homozygous	60	1%
Unknown	47	1%
Heterozygous>Non-familial>Heterozygous	24	0.54%
Homozygous>Non-familial>Homozygous	22	0.49%
Heterozygous>Homozygous>Heterozygous	20	0.45%
Heterozygous>Non-familial>Heterozygous>Non-familial	16	0.36%
Homozygous>Heterozygous>Homozygous>Heterozygous	12	0.27%
Non-familial>Heterozygous>Non-familial	12	0.27%
Homozygous>Non-familial>Heterozygous	11	0.25%
Heterozygous>Non-familial>Homozygous	9	0.20%
Non-familial>Homozygous>Non-familial	9	0.20%
Homozygous>Heterozygous>Non-familial	8	0.18%
Homozygous>Non-familial>Homozygous>Non-familial	8	0.18%
Heterozygous>Homozygous>Non-familial	6	0.13%
Non-familial>Homozygous>Non-familial>Homozygous	6	0.13%

Note: Prescriptions with an unknown indication have been ignored

Table 4 above summarises the number of patients with each indication sequence, where the number of patients is higher than 5. The total number of patients treated with evolocumab since listing on the PBS is 4,483. The proportion of patients in the top three indication sequences, i.e. Homozygous, Non-familial, or Heterozygous with no switching of indication was 79% of the total number of treated patients.

Overall utilisation

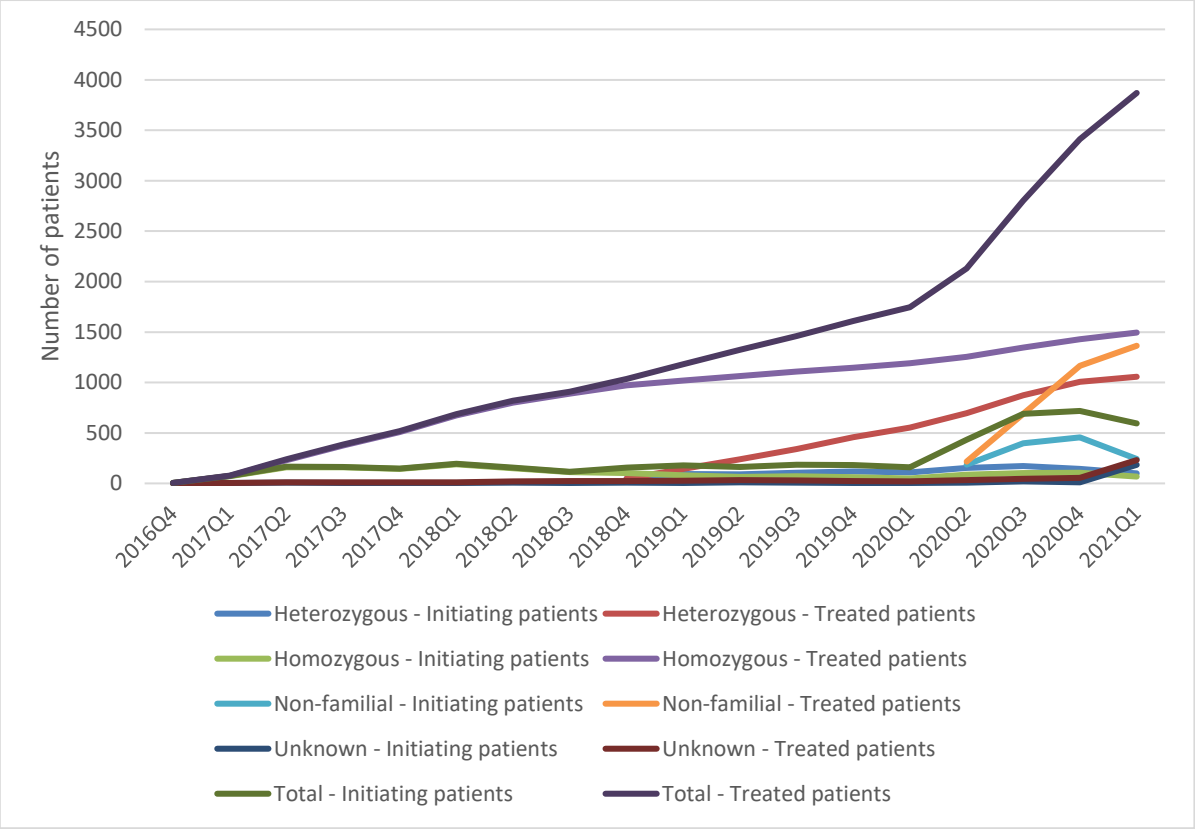

Figure 5: Initiating and treated patients by indication

Note: Indication determined by authority or streamlined code

There appears to be clear increase in the number of treated patients when evolocumab was listed for non-familial hypercholesterolaemia, however as noted in the previous review, the listing of familial heterozygous does not appear to have increased the overall number of treated patients above existing levels.

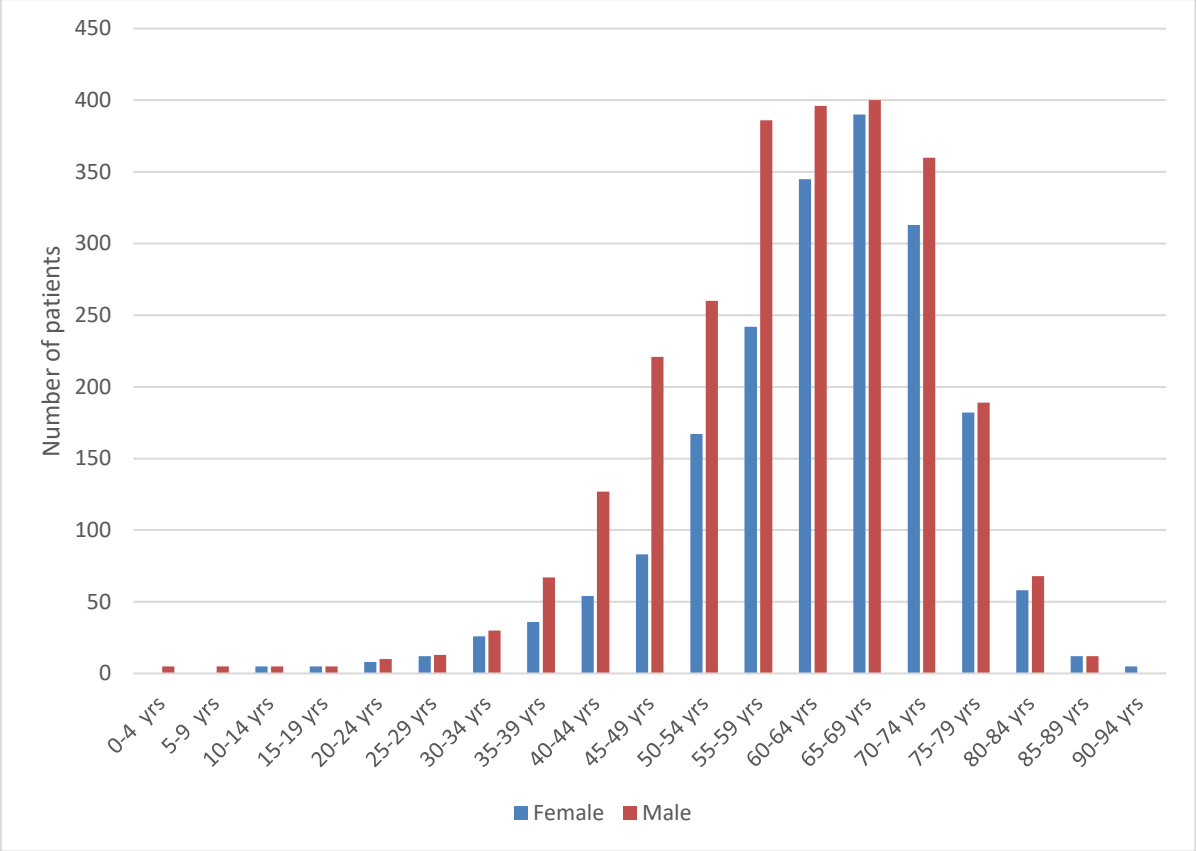

Figure 6: Age and gender of patients at initiation, all indications

Note: patient numbers < 5 are shown as 5.

Table 5: Mean and median age at initiation by main indication

Main indication	Patient sex	N	Mean	Median
Heterozygous	F	568	62.4	64
	M	605	58.5	59
	All	1,173	60.4	61
Homozygous	F	861	60.0	62
	M	975	56.5	57
	All	1,836	58.2	59
Non-familial	F	491	68.1	69
	M	936	65.4	66
	All	1,427	66.4	67
Unknown	F	15	59.3	61
	M	32	64.8	69
	All	47	63.0	65

In all groups a majority of patients are male, however this majority is largest in non-familial hypercholesterolaemia. The mean and median age by main indication suggests that patients with familial homozygous hypercholesterolaemia may be the youngest patients to initiate to evolocumab.

Table 6: Number of treatments by main indication

Main indication	N	Mean	Median	Min	Max
Heterozygous	410	11.1	13	1	18
Homozygous	278	8.8	9	1	17
Non-familial	10	11.3	12	6	13
Unknown	9	4.7	6	1	10
Overall	707	10.1	11	1	18

Note: Cohort who initiated in 2019, followed for one year.

From Table 6, it appears that for patients who initiated treatment with evolocumab in 2019, those patients with homozygous hypercholesterolaemia received the lowest number of treatments per year.

Table 7: Number of prescriptions dispensed by quantity, form and year

		Quantity			
		1	2	3	6
2016	140 mg in 1 mL			7	<5
2017	140 mg in 1 mL	6	268	2,039	75
	420 mg in 3.5 mL	<5			
2018	140 mg in 1 mL	32	534	6,357	123
	420 mg in 3.5 mL	250	20	5	<5
2019	140 mg in 1 mL	39	3,560	7,998	134
	420 mg in 3.5 mL	841	40	6	<5
2020	140 mg in 1 mL	77	12,136	9,086	114
	420 mg in 3.5 mL	3082	89	7	

Note: Quantities of 5 and >6 are not shown due to small numbers. Small cell counts for other quantities have been confidentialised.

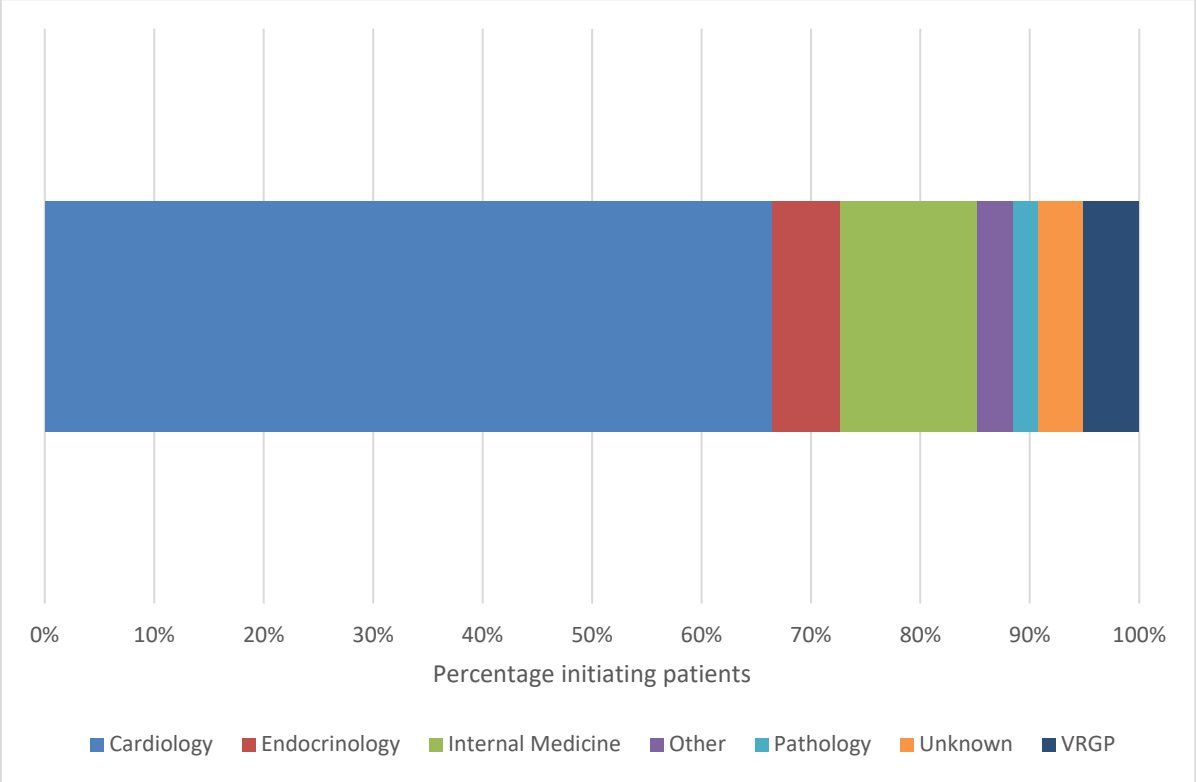

Figure 7: Proportion of patients initiating evolocumab by prescriber type in 2020

Figure 7 depicts the type of prescribers who initiated PBS subsidised evolocumab for any indication in 2020. The largest proportion of patients initiating evolocumab had their first prescription written by a cardiologist; followed by endocrinologists and internal medicine specialists.

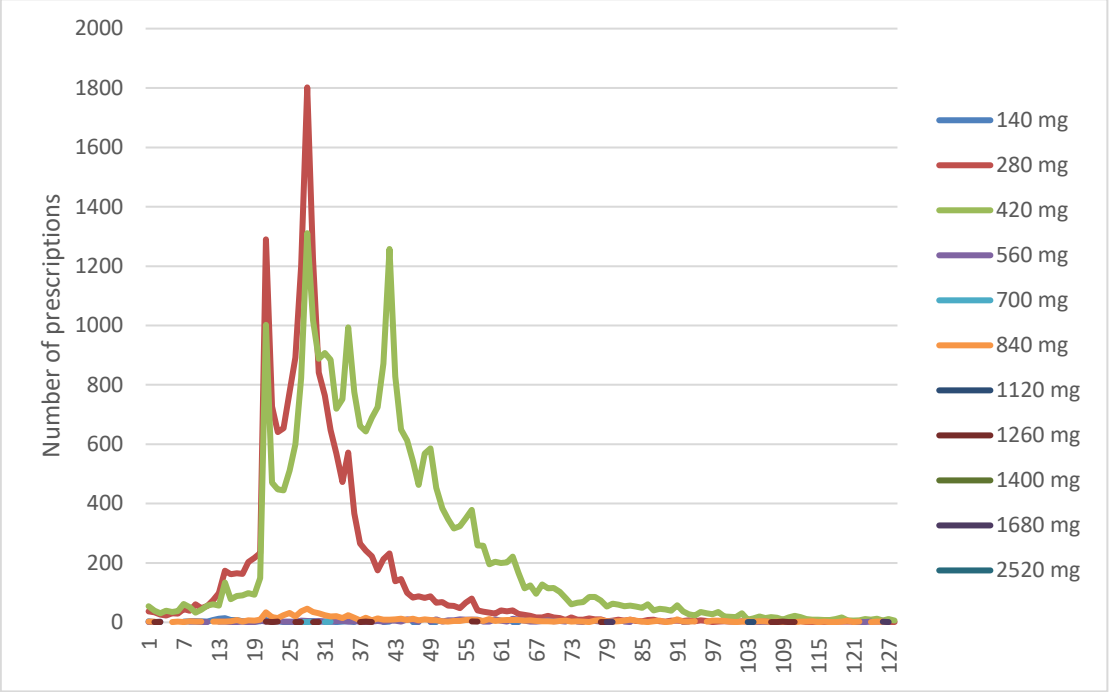

Figure 8: Distribution of time to next supply by dose supplied, all indications

As noted in Table 1, the recommended dosage of evolocumab for primary hypercholesterolaemia is 140 mg every 2 weeks or 420 mg once monthly. For homozygous familial hypercholesterolaemia the recommended initial dose is 420 mg once monthly. These doses may be supplied as one single use pen for a 140 mg dose, or for a 420 mg dose as a single-use automated mini-doser with 3.5 mL pre-filled cartridge or three single-use pre-filled pens administered consecutively within 30 minutes.

From Table 7 it appears there is a high proportion of prescriptions being dispensed with two or three 140 mg pen devices (280 mg or 420 mg). Figure 8 shows the most common refill time for a total dose of 280 mg and 420 mg is 28 days, and that after receiving 420 mg patients are also commonly resupplied evolocumab at 21, 35 and 42 days.

Table 8: Time to next supply by dose supplied

Dose supplied (mg)	N	Mean	Median	Mode	Min	Max
140	152	27.7	17.5	14	1	598
280	18,645	31.0	28	28	1	476
420	30,228	43.4	38	28	1	1,186
560	332	59.1	54	63	1	1,170
700	18	36.3	31.5	24	13	68
840	941	51.5	36	28	1	358
1,120	11	119.7	115		5	180
1,260	73	109.8	104	56	2	469
1,400	11	157.1	165		25	214
1,680	33	122.3	126	51	22	237
Overall	50,471	39.3	33	28	1	1,186

Note: Doses higher than 1,680 mg have been deleted due to small numbers

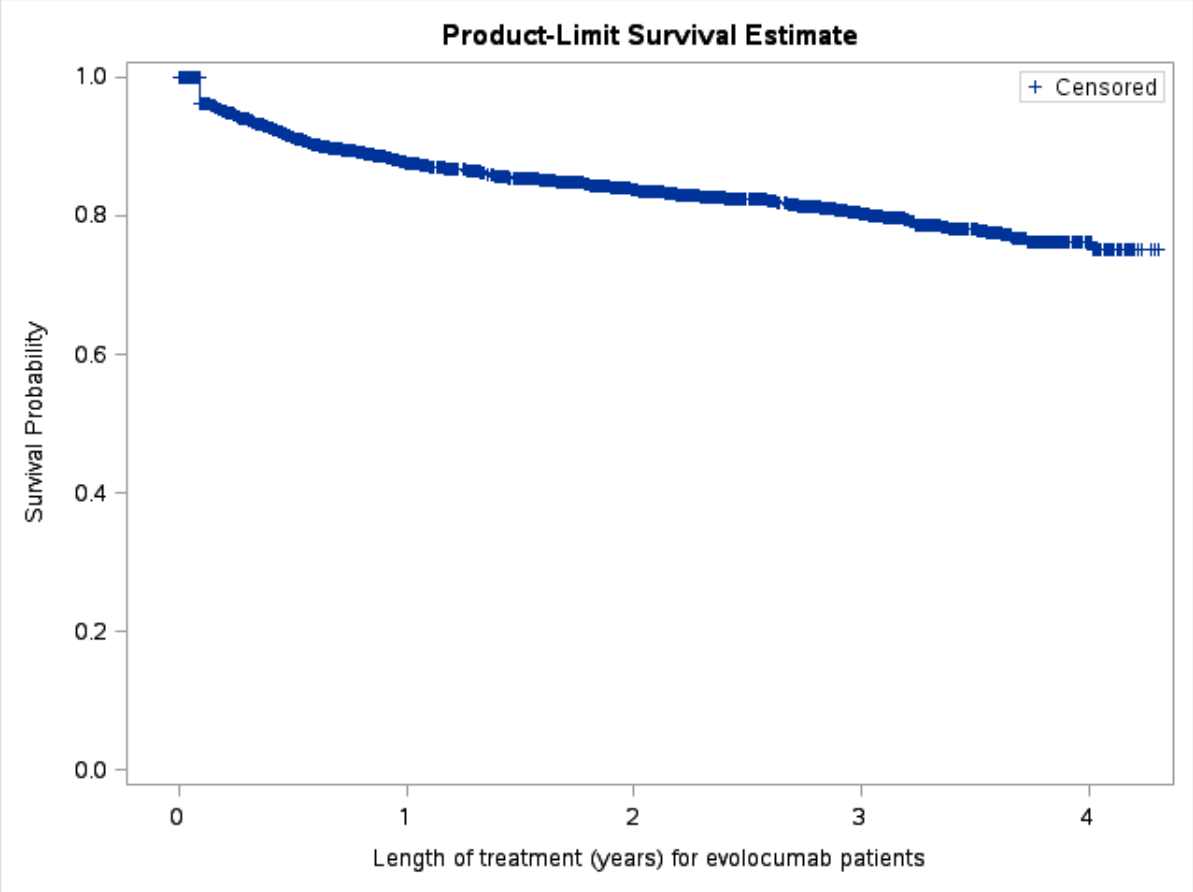

Figure 9: Kaplan-Meier estimates of length of treatment

The data were too immature to assess the treatment duration with evolocumab, the median therapy time had not been reached. As at March 2021, the mean length of treatment was estimated to be 3.24 years with a standard error of 0.02360 years.

Actual versus predicted utilisation

Approach taken to estimate utilisation

The March 2018 submission used an epidemiological approach to estimate the extent of use of evolocumab in the proposed populations. The size of the Australian population sourced from the Australian Bureau of Statistics (ABS) was used as the starting point of the analysis. The prevalence of FH was estimated using Watts et al (2015). Watts et al estimated the probable age standardised prevalence of FH, from an unselected longitudinal survey, as 0.0027, with a confidence interval between 0.0015 and 0.0039.[2] The submission applied a prevalence of 0.00283 (i.e. 1 in 353 persons).

The submission applied a diagnosis rate, percentage of FH patients with ASCVD, percentage of FH patients with LDL-C greater than 3.3 mmol/L, percentage of FH patients with LDL-C greater than 5 mmol/L, and uptake rates between [redacted] and [redacted]. The monthly:fortnightly evolocumab dosing split was assumed to be 20:80.

Analysis of actual versus predicted utilisation

As the March 2018 submission estimated the number of patients who would access PBS evolocumab under heterozygous listing and the extension of the LDL level, the submission estimated all FH patients. This PvA compares estimates of the submission to the actual use of all FH (heterozygous and homozygous) as determined by the indication of the prescription. For comparison, the submission for homozygous FH estimated [redacted] patients would be treated for homozygous FH in year 1, and the actual number was 502. For more details see Appendix B.

The submission labelled this estimation 'prescriptions', however given the multiple quantities being supplied (Table 7) these are shown for prescriptions and for total quantity (quantity × prescriptions).

[2] Watts GF, Shaw JE, Pang J, Magliano DJ, Jennings GLR, Carrington MJ, Prevalence and treatment of familial hypercholesterolaemia in Australian communities, International Journal of Cardiology, Volume 185, 2015, Pages 69-71, https://doi.org/10.1016/j.ijcard.2015.03.027

Table 9: Predicted vs. actual use of evolocumab for heterozygous and homozygous familial hypercholesterolaemia

			2018	2019	2020
Patients		Predicted	[redacted]	[redacted]	[redacted]
		Actual	1,124	1,753	2,693
		% Difference	[redacted]	[redacted]	[redacted]
Prescriptions	140 mg in 1 mL	Predicted	[redacted]	[redacted]	[redacted]
		Actual prescriptions	6,908	11,537	17,181
		% Difference	[redacted]	[redacted]	[redacted]
		Predicted	[redacted]	[redacted]	[redacted]
		Actual quantity	20,545	31,471	43,675
		% Difference	[redacted]	[redacted]	[redacted]
	420 mg in 3.5 mL	Predicted	[redacted]	[redacted]	[redacted]
		Actual prescriptions	274	880	2,268
		% Difference	[redacted]	[redacted]	[redacted]
		Predicted	[redacted]	[redacted]	[redacted]
		Actual quantity	314	952	2,360
		% Difference	[redacted]	[redacted]	[redacted]
	Total services	Predicted	[redacted]	[redacted]	[redacted]
		Actual prescriptions	7,182	12,417	19,449
		% Difference	[redacted]	[redacted]	[redacted]
		Predicted	[redacted]	[redacted]	[redacted]
		Actual quantity	20,859	32,423	46,035
		% Difference	[redacted]	[redacted]	[redacted]

Discussion

The previous evolocumab report in October 2019 noted that the number of patients treated with evolocumab in the first two years of listing was higher than expected. As noted in the 'Previous reviews by the DUSC' section, due to the PBS restriction of this listing, heterozygous patients could have been eligible for PBS treatment under the homozygous listing. The listing of heterozygous hypercholesterolaemia does not appear to have increased the number of initiating or treated patients. However, the listings of non-familial may have (reasonably) increased the number of initiating and treated patients.

Although the previous report noted that the use of evolocumab for HoFH was underestimated, the current predicted versus actual review shows that the number of HeFH patients was overestimated.

The analysis of consistency of utilisation by indication shows that of the 4,483 patients treated with evolocumab since its first listing, 79% have only been treated under only one indication. As streamlined listings and item codes with multiple associated indications were PBS listed in May 2020, this percentage may decrease in the future.

The cohort of patients who initiated in 2019 were supplied a mean number of prescriptions of 10.1, with a median of 11. This includes patients who are treated monthly and fortnightly. The most common dose dispensed in 2020 was 420 mg, and it appears there is a strong preference among either patients or prescribers for multiple 140 mg pen devices, rather than one automated mini-doser with 3.5 mL pre-filled cartridge.

The most common resupply time for 280 mg doses and 420 mg doses was 28 days. However, although a majority of patients were supplied evolocumab once a month, there were also peaks in resupply times of 420 mg at five and six weeks.

Actions undertaken by the DUSC Secretariat

A copy of the report was sent to the sponsor of evolocumab and relevant consumer groups.

DUSC consideration

DUSC noted that the listing of heterozygous hypercholesterolaemia does not appear to have increased the number of initiating or treated patients. DUSC noted the clear increase in the number of supplied prescriptions following the listing of non-familial hypercholesterolaemia on 1 May 2020.

DUSC noted that evolocumab is available in two different doses and devices, a 420 mg automated mini-doser (AMD) with 3.5 mL pre-filled cartridge and 140 mg in 1 mL single-use pre-filled pen device. DUSC noted that evolocumab may be administered fortnightly (140 mg) or monthly (420 mg). DUSC noted that a dose of 420 mg once monthly may be administered by one AMD or three single-use pre-filled pens administered consecutively within 30 minutes. DUSC considered that the number of prescriptions dispensed with

quantities of two and three 140 mg pens was consistent with the recommended fortnightly and monthly dosing. DUSC commented that the majority of patients are receiving the 420 mg dose as three single pens, and questioned why there is a patient preference for this rather than one AMD.

DUSC noted the proportion of patients with consistent coding of indication was 79% of the total number of treated patients. DUSC commented that a high proportion of patients are being approved for evolocumab through a written or telephone Authority Approval (prior to May 2020) or through the Online PBS Authorities system (after May 2020). DUSC considered this is likely because the maximum quantity of the 140 mg pen devices on the non-familial and familial heterozygous hypercholesterolaemia listings is two. DUSC commented that patients who require three pen devices for a monthly treatment would need to seek an increased quantity through an Authority Approval.

DUSC noted analyses by age and gender which showed the majority of patients are male, and the highest proportion of male and female patients supplied evolocumab was 65-69 years old. DUSC noted that the analysis of age by indication suggested that patients with familial homozygous hypercholesterolaemia appear to be the youngest patients to initiate evolocumab. DUSC commented that the analysis of age generally matches with expectations, however patients with homozygous hypercholesterolaemia may have been expected to be younger. DUSC recalled that at the time of the March 2018 submission, DUSC and the sponsor disagreed over the population to which the prevalence of familial hypercholesterolaemia should be applied. DUSC considered that the familial hypercholesterolaemia prevalence should be applied to the population aged above 25 years (DUSC Advice November 2017) whereas the resubmission applied the prevalence rate to the whole Australian population.[3] DUSC noted that the data shows there are less than 130 patients younger than 35 who have initiated evolocumab.

DUSC noted that the estimates in the predicted versus actual analysis estimated the use of familial hypercholesterolaemia, and the actual numbers presented both quantity and prescriptions. DUSC commented that as three pen devices are often used for a dose of 420 mg, quantity was a better comparison than prescriptions. DUSC commented that the use of evolocumab to treat homozygous hypercholesterolaemia was underestimated, but some of the apparent overuse for homozygous hypercholesterolaemia and underuse for heterozygous hypercholesterolaemia may be due to inaccurate assignment of the relevant streamlined authority codes.

Regarding the predicted versus actual comparison, the sponsor in its Pre-Sub-Committee Response (PSCR) stated that, [redacted]

[3] Evolocumab Public Summary Document, March 2018, p9, https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2018-03/files/evolocumab-psd-march-2018.pdf

[redacted]

DUSC agreed that clinics are busy but evolving, and considered that opening prescribing to GPs at this stage would not be appropriate. DUSC considered that the proportion of patients initiating evolocumab by prescriber type in 2020 as presented in the report appears appropriate.

The PSCR also noted, "That a submission requesting reconsideration of GP initiation was rejected at the November 2020 PBAC meeting and the sponsor intends to revisit this request in a submission for the March 2022 meeting, which is within the PBAC's advised timeline (18-24 months post-listing) of when DUSC would review utilisation under the non-familial ASCVD listing." DUSC commented that there is a lag in predicted versus actual reviews due to data processing, and as the non-familial listing was added to the PBS 1 May 2020, it would be due for DUSC review at the February 2023 meeting.

DUSC noted the analysis of the estimated length of treatment showed the data was too immature to assess the treatment duration with evolocumab and the median therapy time had not been reached. DUSC noted there was some drop off in patients immediately after initiation, but commented that many patients are continuing treatment for up to four years, noting that the total time of captured in the data extract was four years and four months.

DUSC actions

DUSC requested that the report be provided to the PBAC for consideration.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsors' comments

Amgen: The sponsor has no comment.

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

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Appendix A

PBAC Meeting	Indication Considered	Outcome
March 2015	Hypercholesterolaemia	The PBAC rejected the request to list evolocumab for the treatment of hypercholesterolaemia on the basis of unestablished clinical place in therapy and the uncertainty surrounding its use in clinical practice. The PBAC noted that the submission was made under the TGA-PBAC parallel process with the TGA Delegate's consideration expected in late 2015. Accordingly, the PBAC noted that there were no TGA documents available during the time of PBAC consideration to determine the indication of the drug and its clinical place in therapy.
March 2016	Familial hypercholesterolaemia	The PBAC recommended the Authority Required listing of evolocumab under Section 85, for the treatment of homozygous familial hypercholesterolaemia. In making this recommendation, the PBAC considered that the homozygous FH population (with an abnormality in both of the two copies of the specific gene) represent a small, definable, patient group, in whom there is a high level of clinical need.
July 2017	Familial homozygous hypercholesterolaemia (listing of Injection 420 mg in 3.5 mL single dose autoinjector)	The PBAC recommended the listing of the new strength of evolocumab for the treatment of familial homozygous hypercholesterolaemia. The PBAC accepted that this additional form of evolocumab would provide patients with an alternative dosing schedule to the currently listed form at no additional cost to the Government.
November 2017	Familial hypercholesterolaemia (extension of the listing to include the treatment of HeFH)/ hypercholesterolaemia with symptomatic atherosclerotic cardiovascular disease (ASCVD) who do not have underlying FH	The PBAC deferred making a recommendation to extend the PBS listing of evolocumab for patients with familial hypercholesterolaemia in order to address the residual uncertainty with the economic model following revisions provided in the pre-PBAC response. The PBAC did not recommend the listing of evolocumab for patients with non-familial hypercholesterolaemia with atherosclerotic disease on the basis of a high incremental cost effectiveness ratio (ICER) and high and uncertain patient population numbers.
March 2018	Familial hypercholesterolaemia	The PBAC recommended extending the PBS listing for evolocumab for patients with Familial Hypercholesterolaemia to include patients with heterozygous FH, under certain conditions. 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 considered that the revised economic model, reduced price and other arrangements proposed in the resubmission addressed the

PBAC Meeting	Indication Considered	Outcome
		outstanding issues raised by the PBAC from the November 2017 submission.
July 2018	Non-familial hypercholesterolaemia with atherosclerotic disease.	The PBAC did not recommend the listing of evolocumab for patients with non-familial hypercholesterolaemia with atherosclerotic disease on the basis of an inadequately defined patient population, an uncertain incremental cost-effectiveness ratio (ICER) and high and uncertain patient population numbers. The PBAC considered that this population required more refined eligibility criteria in the proposed PBS listing given the very high financial estimates.
July 2019	Hypercholesterolaemia	The PBAC deferred making a recommendation on the listing of evolocumab for the treatment of non-familial hypercholesterolaemia in patients with ASCVD and additional high-risk factors. The PBAC also deferred making a recommendation on the resubmission's request to extend the existing familial hypercholesterolaemia listing in the ASCVD population to include patients with low-density lipoprotein (LDL) levels between 2.6 mmol/L and 3.3 mmol/L.
November 2019	Non-familial hypercholesterolaemia with atherosclerotic disease and an extension for familial hypercholesterolaemia 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.	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.
November 2020	To allow general practitioners (GPs) to initiate treatment, but only after having consulted a specialist.	The PBAC did not recommend an amendment to the Authority Required listings of evolocumab for all indications to allow GPs to initiate treatment after having consulted a specialist. The PBAC advised that "Must be treated by a specialist physician" for initiation of treatment should remain for all indications, consistent with its previous advice.

Appendix B

Analysis of actual versus predicted utilisation - October 2019 report

A comparison of the predicted utilisation of evolocumab for HoFH versus actual use is shown in Table B.

Table B: Evolocumab: actual versus predicted utilisation for HoFH

		Year 1	Year 2
Patients	Predicted	[redacted]	[redacted]
	Actual	502	1,068
	%Difference	[redacted]	[redacted]
Prescriptions (total)	Predicted	[redacted]	[redacted]
	Actual	2,010	6,915
	%Difference	[redacted]	[redacted]
Prescriptions for 140 mg in 1 mL pen device (10958R)	Predicted	[redacted]	[redacted]
	Actual	2,010	6,686
	%Difference	[redacted]	[redacted]
Prescriptions for 420 mg in 3.5 mL cartridge (11193D)	Predicted	n/a	[redacted]
	Actual	n/a	229
	%Difference	n/a	[redacted]
Expenditure	Predicted	[redacted]	[redacted]
	Actual	$1,848,635	$6,319,473
	%Difference	[redacted]	[redacted]

Source: Evolocumab Final Estimates 2016 (predicted), DHS prescription database (actual), extracted July 2019.
n/a = not applicable.
Note: Expenditure is reported based on published prices. Special Pricing Arrangements apply.
*From the July 2017 PBAC submission for listing of the 420mg in 3.5mL pre-filled cartridge

The sponsor's predicted number of patients, prescriptions and expenditure were very similar between listing years 1 and 2; i.e. the sponsor predicted very little growth in the market. The actual number of patients receiving evolocumab was higher than predicted in both year 1 and year 2. The number of PBS subsidised prescriptions of evolocumab was close to the predicted number in Year 1 but was higher than predicted in year 2 of listing. The government expenditure was lower than predicted in the first year of listing but was higher than expected in the second year of listing.

In the July 2017 submission, the sponsor estimated that the 420 mg in 3.5 mL pre-filled cartridge would substitute for 2% of the 140 mg in 1 mL pre-filled pen prescriptions. Actual data show that the cartridge accounted for 3% of the market in its first year of listing (i.e. the second year of evolocumab listing), although use of both forms was higher than expected.