Comments on the outcomes report for the ezetimibe post-market review stakeholder forum

Merck Sharp & Dohme (Australia) Pty Limited **25 November 2016**

MSD appreciates the opportunity to respond to the minutes of the stakeholder forum, held on 11th November 2016. As we discussed during the forum, MSD would like to contribute some further data and interpretation on the key questions that the expert group posed to the forum.

TOR 1 – Utilisation:

- The 15% of ezetimibe initiations without prior statin/LLT use represents <2% of patients initiated to LLT therapy, a figure lower than the lowest estimates of statin intolerance
- Cohort 1 (no statins in preceding 2 years) would be much smaller if a look-back window of 8 years was used and the analysis was able to identify patients purchasing statins privately. Cohort 1 is confounded as it includes patients with statin intolerance, and the denominator used to calculate the proportion with contraindications is incorrect
- It was claimed that a large part of Cohort 2 did not have a dose adjustment – this did not consider patients who were at their maximally-tolerated dose, or those who had a dose change 2 or more years before or one that was paid for as a private script
- Ultimately, the presented data does not suggest significant use outside PBS restrictions

TOR 2 – Guidelines:

- Silverman et al. 2016 was not intended to explore sequencing of statin and non-statin therapies, and the authors concluded that "*…when tolerated, statins should be the first-line therapy*"; guidelines updated after IMPROVE-IT still support and recommend statins as first-line treatment
- The fact that ezetimibe use is largely within the restrictions suggests that the existing eligibility criteria are appropriate and consistent with best practice treatment; changing them is unlikely to alter utilisation patterns

TOR 3 – Studies:

- IMPROVE-IT validates the use of LDL-C as a surrogate for the reduction in risk of major vascular events; however, it does not follow that the mechanism by which LDL-C is reduced "*is not relevant*"; by validating the use of LDL-C, IMPROVE-IT confirms that PBAC's recommendation to list ezetimibe on the basis of a surrogate measure was correct, and the predicted reduction in events would occur in clinical practice
- The conclusion that "*outcomes [of key clinical studies] are either inconclusive or not generalisable to the Australian population*" is inconsistent with previous decisions, as these were the same studies that were previously accepted by the PBAC as being suitable to support Government subsidy – more recent evidence, such as IMPROVE-IT, adds to this body of evidence

1. TERM OF REFERENCE ONE – UTILISATION

The purpose of TOR 1 was to review current utilisation of Pharmaceutical Benefits Scheme (PBS) - listed ezetimibe and ezetimibe combination products. The approach used by the Evaluation Group was presented in some detail in the Issues Paper dated November 2016 (page 8). The analyses relied on evidence of utilisation from the period 1 April 2014 to 1 April 2015, during which time 45,645 patients were initiated on ezetimibe monotherapy or in combination with a statin. These patients were categorised into two distinct groups:

- **Cohort 1** – no history of a statin or other LLT in the previous two years (15% of patients)
- **Cohort 2** – a history of a statin or other lipid-lowering therapy (LLT) in the previous two years (85% of patients)

Cohort 1: It was claimed that this group, described as "the proportion of patients initiating on ezetimibe without a prior history of statin or other LLT", is much larger than that expected from the reported incidence of contraindications to statins. It was suggested that this could be due to "significant use outside PBS restrictions" or "a prior history of statins or other LLTs beyond the two years prior to the study period".

Cohort 1 would be a third smaller if it excluded patients with a prior history of statins / LLT before the 2 year look-back window:

- The utilisation analysis conducted by the Evaluation Group selected an insufficient look-back period of two years. MSD has replicated this analysis with a 10% concessional sample but increased the look-back period to a maximum of 8 years (see Appendix 1). A look-back period of 8 years is reasonable given this is a mature, well-established market. MSD's analysis shows:
  - Using a look-back period of 2 years, around 14% of patients would not have a prior history of statin / LLT – this is similar to the 15% identified by the evaluation group
  - The proportion of patients without a prior history of statin / LLT decreases as the look-back period is increased, meaning a large of patients claimed not to have a history of statin / LLT, were incorrectly categorised into Cohort 1
  - With a look-back period of 8 years, only 8% of patients would not have a history of statin / LLT prior to initiating ezetimibe

Patients in Cohort 1 could have a prior history of statin / LLT which was not picked up in the analysis, for example because they paid for statin therapy privately:

- The price of some statins first fell below the general co-payment in 2005 – first for some simvastatin and fluvastatin strengths, followed by pravastatin in 2007, and atorvastatin

and rosuvastatin in 2012[1]. These medicines would be typically funded by patients and usage would not be picked up in the analyses presented by the evaluation group, meaning that these patients were incorrectly categorised into Cohort 1

- It has been reported that under co-payment utilisation for statins was 3.3% in the financial year 2012-13[2], increasing to 7.5% in 2013-14[3].

Cohort 1 is not restricted to patients with a contraindication to a statin – it includes other identifiable patient groups, in particular those with statin intolerance, which is a large group, the size of which is often underestimated:

- Cohort 1 is <u>not</u> a homogenous group solely made up of patients with contraindications to a statin; it also includes patients with homozygous sitosterolaemia (Streamline Code 5563) and those that developed a clinically important product-related adverse event during treatment with a statin necessitating withdrawal of the statin treatment (Streamline Code 5562). In order to quantify the number of patients treated with ezetimibe and have a contraindication to a statin, the analyses should have been restricted to Streamline Code 5576.
- RCTs report an incidence of statin intolerance of around 5% or greater[4,5], for example:
    - The STOMP study[6] of statin-naïve patients used very tight definitions of statin myalgia – 10% had definite myalgia on atorvastatin 80mg
    - Muscle symptoms (pain, stiffness or weakness) were found in 16% of patients in JUPITER
- In clinical practice, the rates are often higher – observational studies suggest up to 20% of patients experience statin-associated symptoms[7,8].

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[1] Thai LP, Moss JR, Godman B, Vitry AI. Cost driver analysis of statin expenditure on Australia's Pharmaceutical Benefits Scheme. Expert Rev Pharmacoecon Outcomes Res. 2016 Jun;16(3):419-33.
[2] Australian Government Department of Health, Report to Parliament on the Collection of PBS/RPBS Under Co-payment Prescription Data 2012-13. [cited 2015 Feb 15]. Available from: https://www.health.gov.au/internet/main/publishing.nsf/Content/
[3] Australian Government Department of Health. Report on the Collection of Under Co-payment Data 2013–2014. 2015. [Cited 15 February 2015]. Available from: http://www.pbs.gov.au/info/statistics/under-co-payment/ucpdata-report.
[4] G. Fernandez, E.S. Spatz, C. Jablecki, P.S. Phillips, Statin myopathy: a common dilemma not reflected in clinical trials, Cleve Clin. J. Med. 78 (2011) 393e403.
[5] H. Zhang, J. Plutzky, S. Skentzos, et al., Discontinuation of statins in routine care settings: a cohort study, Ann. Intern Med. 158 (2013) 526e534.
[6] Parker BA, Capizzi JA, Grimaldi AS, Clarkson PM, Cole SM, Keadle J, Chipkin S, Pescatello LS, Simpson K, White CM, Thompson PD. Effect of statins on skeletal muscle function. Circulation. 2013 Jan 1;127(1):96-103.
[7] G. Fernandez, E.S. Spatz, C. Jablecki, P.S. Phillips, Statin myopathy: a common dilemma not reflected in clinical trials, Cleve Clin. J. Med. 78 (2011) 393e403.

- Ultimately, it is the "perception" of the patient that is clinically important – and the determinant of patient adherence to therapy, not any specific "diagnostic" definition of muscle intolerance.
- Ultimately, 5-10% of patients treated with a statin are categorised to be statin intolerant[9,10,11] - in Australia, this would translate to up to 260,000 patients[12].

The denominator used to calculate the proportion of patients with contraindications to statins (claimed to be 15%) is incorrect:

- As per the above two points, the size of Cohort 1 cannot be relied on to accurately estimate the size of the population who are contraindicated to a statin
- Regardless, the proportion representing those contraindicated to statin therapy needs to be calculated versus the entire population of patients eligible to use LLT therapy, not merely those starting treatment with ezetimibe. In 2010-11, there were 2.6m patients taking a statin[13]. Even if all the patients in Cohort 1 were on ezetimibe monotherapy, this would represent <2% of those on a statin and the overall eligible LLT population.

The available data does not suggest significant use outside PBS restrictions

- MSD does not believe there is an issue with utilisation outside the restriction for ezetimibe. Ezetimibe use should be considered in 2 distinct patient populations reflective of PBS subsidy, namely; as monotherapy in patients contraindicated or intolerant to statin therapy and as adjunctive therapy for patients inadequately controlled on maximum tolerated dose of a statin. There are currently approx. 64,000 patients treated on monotherapy and 240,000 taking ezetimibe as part of a combination with various statins.
- Included in MSD's submission to the TOR were the following conclusions:
  - Based on a review of a 10% PBS concessional patient dataset available to MSD over 88% of patients initiated with ezetimibe in the form of FDC / co-pack complied with

[8] H. Zhang, J. Plutzky, S. Skentzos, et al., Discontinuation of statins in routine care settings: a cohort study, Ann. Intern Med. 158 (2013) 526e534.
[9] G. Fernandez, E.S. Spatz, C. Jablecki, P.S. Phillips, Statin myopathy: a common dilemma not reflected in clinical trials, Cleve Clin. J. Med. 78 (2011) 393e403.
[10] R.K. Nair, R.L. Karadi, E.S. Klipatrick, Managing patients with 'statin intolerance': a retrospective study, Br. J. Cardiol. 15 (2008) 158e160.
[11] H. Zhang, J. Plutzky, S. Skentzos, et al., Discontinuation of statins in routine care settings: a cohort study, Ann. Intern Med. 158 (2013) 526e534.
[12] http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2012-07/review-of-statin-therapies
[13] http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2012-07/review-of-statin-therapies

the PBS criteria of having >3 historical statin scripts at the same dose (thus maximum tolerated dose).

- Only 3.3% of patients initiated onto ezetimibe with no record of previous statin use.

- Moreover, the minimal use outside of the restriction could be explained and would be clinically appropriate. For example due to media concerns (e.g. Catalyst), patients may have refused to receive a statin – they would have still required LDL lowering therapy. Cessation of statin treatment is known to be associated with worse cardiovascular outcomes. A large meta-analysis of 15 studies showed that the risk of death was increased by almost half (45% increase in all-cause mortality) in patients taking <80% of their prescribed statin therapy when compared to patients who were more adherent[14]. Thus use of ezetimibe would have been clinically appropriate.

Cohort 2: In the Issues Paper, it was noted that approximately 70% of patients in this cohort had not changed their statin dose in the preceding 2 years.

Patients in Cohort 2 might already be at their maximally-tolerated statin dose – increasing the statin dose would not be clinically appropriate:

- The Issues Paper seems to suggest that patients who did not have a dose adjustment in the preceding 2 years are not at their maximally tolerated dose; this fails to recognise that these patients might have already been at their maximally tolerated dose, and that this is the main reason why they did not have a dose adjustment in the preceding 2 years. For example, patients might have reported mild tolerability issues – observational studies suggest up to 20% of patients experience statin-associated symptoms[15,16]. Increasing the dose in these patients would risk exacerbating existing symptoms which could in turn lead to compliance and/or persistence issues.
- Statins are being used at higher and higher doses. An analysis of statin utilisation in Australia published this year identified increasing prescribing of higher strength statins

[14] Chowdhury R, Khan H, Heydon E, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J 2013;34:2940–8.
[15] G. Fernandez, E.S. Spatz, C. Jablecki, P.S. Phillips, Statin myopathy: a common dilemma not reflected in clinical trials, Cleve Clin. J. Med. 78 (2011) 393e403.
[16] H. Zhang, J. Plutzky, S. Skentzos, et al., Discontinuation of statins in routine care settings: a cohort study, Ann. Intern Med. 158 (2013) 526e534.

over time, and suggested that this could be a result of clinical guidelines advocating tighter control of cholesterol levels[17]

- Similar conclusions were made in the Statin Review, which reported rapid uptake of higher strength statins[18]
- MSD's analyses show that the vast majority of patients are on higher statin doses before they have ezetimibe added in – around 8 in 10 patients are initiated onto combination therapy from a statin dose that is equivalent to simvastatin 40 mg or higher (see below).

Table: Ezetrol and Eze FDC initiations

	No recent statin use	Simva 5 mg	Simva 10 mg	Simva 20 mg	Simva 40 mg	Simva 80 mg	Simva 160 mg	Grand Total
Vytorin	18.23% 801 0%	0.11% 5 60%	1.21% 53 55%	6.49% 285 67%	26.02% 1,143 83%	30.21% 1,327 92%	17.73% 779 92%	100.00% 4,393 71%
Atozet	7.81% 84 0%		0.09% 1 0%	3.44% 37 57%	13.75% 148 66%	38.29% 412 88%	36.62% 394 93%	100.00% 1,076 79%
Rosuzet	6.11% 24 0%			8.91% 35 66%	17.05% 67 76%	32.57% 128 91%	35.37% 139 90%	100.00% 393 80%
Ezetrol + statin	5.78% 178 0%	0.03% 1 100%	0.84% 26 46%	8.93% 275 76%	21.40% 659 84%	29.29% 902 89%	33.73% 1,039 94%	100.00% 3,080 83%
Grand Total	12.16% 1,087 0%	0.07% 6 67%	0.89% 80 51%	7.07% 632 70%	22.56% 2,017 82%	30.97% 2,769 90%	26.29% 2,351 93%	100.00% 8,942 76%

This analysis includes every patient's first ever Ezetrol script and their first ever Ezetimibe FDC script
Recent statin doses are classified as being in the previous 12 months
This analysis is based on concessional patients only

- This information supports the conclusion that patients are up-titrated with statins consistently and appropriately, before being initiated to ezetimibe add-on therapy

Patients in Cohort 2 could include patients who had a change in statin dose which preceded the 2 year look-back window used in the analysis:

- The utilisation analysis conducted by the Evaluation Group selected an insufficient look-back period of 2 years. Similar to the analyses presented earlier, extending the look-back period to 8 years should result in a larger proportion of patients having a change in their statin dose. This is important to capture, as it could be possible that the dose that they were on was already their maximally-tolerated dose as argued above

[17] Thai LP, Moss JR, Godman B, Vitry AI. Cost driver analysis of statin expenditure on Australia's Pharmaceutical Benefits Scheme. Expert Rev Pharmacoecon Outcomes Res. 2016 Jun;16(3):419-33.
[18] Statin Review 2012. Available: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2012-07/review-of-statin-therapies

Patients in Cohort 2 could have had a change in statin dose which was not picked up in the analysis, for example because they were changed to a lower strength statin that would have been paid for privately:

- As discussed previously, the price of some statins first fell below the general co-payment in 2005, and the first to fall below this threshold were the lower strength statin packs
- It is possible that patients in Cohort 2 had a change in dose to a lower strength statin, for example because of tolerability issues, which resulted in that script being filled privately. From the information shared to date, it would appear that the methodology applied by the Evaluation Group would have incorrectly classified these patients as not having a dose adjustment.

2. TERM OF REFERENCE TWO – GUIDELINES

In its review of clinical guidelines for the purposes of TOR 2, the Evaluation Group noted that guidelines recommend using statins as first line therapy (i.e. reserving ezetimibe for second line use or in patients intolerant / contraindicated to statins), and attributed this to the very large body of evidence on the clinical benefits of statin use compared to the limited data on patient-relevant outcomes for ezetimibe.

It was noted that Silverman et al. suggests that the order of lipid lowering therapy is not important, and the Reference Group was questioned on ezetimibe's continued position as second line therapy and whether the GSLLD needed to be revised.

Silverman et al. 2016 was not intended to explore sequencing of statin and non-statin therapies

- This systematic review was not intended to address the question of whether statin or non-statin therapies should be used first; the purpose was to explore the relationship between LDL-C lowering and CV outcomes between statin and non-statin therapies
- The conclusion of this review was that statins and non-statin therapies that act through up-regulation of LDL receptor expression are associated with similar cardiovascular risk reduction per decrease in LDL-C

Silverman et al. 2016 did not suggest that "…**the order of lipid lowering therapy used to achieve a reduction in LDL-C is not important"; on the contrary, the authors concluded that "…when tolerated, statins should be the first-line therapy":**

- It is not clear where the claim that the order of lipid therapy is not important came from – MSD could not locate this in the cited publication
- On the contrary, the authors of the study support the recommendations of guidelines to use statins as first-line therapy when tolerated

Guidelines updated after the publication of the IMPROVE-IT trial still support statins as first-line treatment for lowering LDL-C:

- For example, in the latest update of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines for the Management of Dyslipidaemias published in 2016, the ESC/EAS Task Force evaluated the latest evidence including the recently published IMPROVE-IT trial, and made the following recommendations:

Table 16 Recommendations for the pharmacological treatment of hypercholesterolaemia

Recommendations	Class [a]	Level [b]	Ref [c]
Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.	I	A	62, 64, 68
In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.	IIa	C	239, 256, 257
If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	IIa	B	63
If the goal is not reached, statin combination with a bile acid sequestrant may be considered.	IIb	C	
In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	IIb	C	115, 116

LDL-C = low-density lipoprotein-cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

- Taken together with other studies such as the PRECISE-IVUS study, IMPROVE-IT supports the proposal that ezetimibe should be used in patients intolerant to statins or

with contraindications to these drugs, or as second-line therapy in association with statins when the therapeutic goal is not achieved at the maximally tolerated statin dose.

The recommendation that statins should be used as first-line agents is not only because of the large amount of data on the clinical benefits of statin use compared to the limited data on patient-relevant outcomes for ezetimibe:

- IMPROVE-IT was considered a seminal piece of research because it was the first robust, appropriately designed study to confirm that the relationship between LDL-C reduction and outcomes that was well accepted for statins[23], applies equally to ezetimibe
- The main conclusion from the Silverman et al. 2016 was in fact this - that statin and non-statin therapies that work through up-regulation of LDL receptor expression (e.g. ezetimibe) are associated with similar CV risk reduction per decrease in LDL-C
- The fact that guidelines continue to recommend that the existing sequence of statins and ezetimibe remains unchanged is not driven by the lack of data – IMPROVE-IT confirms that validity of CV reduction claims made on the basis of LDL-C lowering. The existing positioning is due to other factors, including:
    - the large reductions observed for LDL-C – at maximal doses statins can provide 30-50% LDL-C lowering, compared to 15-20% with ezetimibe
    - the excellent safety profile and longer history of use of statins
    - the demonstrated clinical benefit of statins
    - the low cost of statins

The fact that ezetimibe use is largely within the PBS restrictions suggests that the existing eligibility criteria are appropriate and consistent with best practice treatment

Altering the eligibility criteria for lipid therapies and/or ezetimibe is unlikely to alter utilisation patterns

- As Prof Sansom suggested, lipid lowering therapies are a mature market:
    - therapeutic choices have been established over more than a decade – it is highly unlikely that prescribing habits will change if restrictions are simplified
    - worldwide use and listings of EZE have been consistent and promotion aligned to this

[23] Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol. Lancet. 2010;376(9753):1670-1681..

This means that the ezetimibe-treated population will continue to be composed of two distinct groups – those who have contraindication to or cannot tolerate a statin, and those who are uncontrolled on a maximally tolerated dose of a statin:

- The comparator for the purposes of presenting an economic analysis continues to be consistent with that accepted by the PBAC:
    - Contraindication to or cannot tolerate a statin – cholestyramine
    - Uncontrolled on a maximally tolerated dose of a statin – placebo

Altering the eligibility criteria for ezetimibe could lead to more patients not achieving target, and would be inconsistent with Quality Use of Medicines principles

- As mentioned previously, statins can result in greater reductions in LDL-C, primarily due to the ability to up-titrate to higher doses
- If restrictions are changes to allow clinicians to use ezetimibe as a first line treatment, it could result in patients being started on a treatment that is less likely to achieve the required reduction in LDL-C levels – this creates a risk that more patients would be under-treated (e.g. due to clinician inertia, or lack of monitoring)

3. TERM OF REFERENCE THREE – STUDIES

It was noted that the findings from the review of the studies demonstrated that outcomes are either inconclusive or not generalisable to the Australian population. Furthermore, the Reference noted that IMPROVE-IT trial confirms the acceptability of the absolute reduction in LDL-C as a valid surrogate for the reduction of the relative risk of major vascular events, and that the mechanism by which LDL-C is reduced is not relevant and there is no strong evidence for a particular order of use of LLT other than the greater body of evidence for statin use.

By validating the use of LDL-C as a surrogate measure, IMPROVE-IT confirms that PBAC's recommendation to list ezetimibe on the basis of a surrogate measure was correct, and the predicted reduction in events would occur.

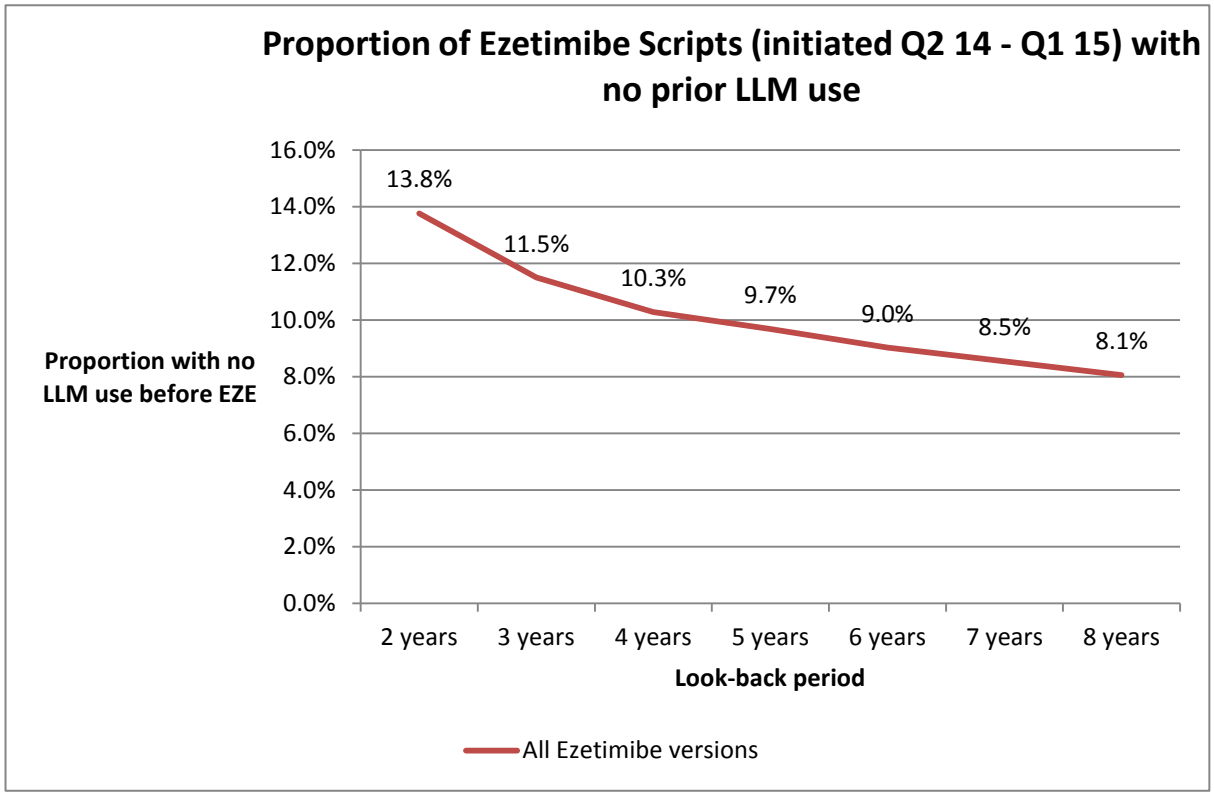
- Notwithstanding the conclusions from Silverman et al. 2016, which are consistent with those of the Review Group, the authors still endorsed the position that ezetimibe should be used as a second-line treatment or in patients who cannot tolerate / are contraindicated to a statin

The conclusion that "outcomes [of key clinical studies] are either inconclusive or not generalisable to the Australian population" is difficult to comprehend, as these were

the same studies that were previously accepted by the PBAC as being suitable to support Government subsidy – more recent evidence, such as IMPROVE-IT, adds to this body of evidence.

- The basis for previous PBAC recommendations has been made with regard to the current 2nd line listing of ezetimibe on the PBS. Treatment efficacy was based on a meta-analysis of 19 trials, evidence which was initially presented in the ezetimibe PBAC submission to the November 2006 PBAC meeting.

APPENDIX 1


Proportion of Ezetimibe Scripts (initiated Q2 14 - Q1 15) with no prior LLM use
Proportion with no LLM use before EZE
16.0%
14.0%
12.0%
10.0%
8.0%
6.0%
4.0%
2.0%
0.0%
13.8%
11.5%
10.3%
9.7%
9.0%
8.5%
8.1%
2 years
3 years
4 years
5 years
6 years
7 years
8 years
Look-back period
All Ezetimibe versions