# 9.01 POST-MARKET REVIEW OF EZETIMIBE

*Commercial-in-Confidence information has been redacted.*

## 1. THE REVIEW

The Post-market Review of Ezetimibe has been conducted as part of the Australian Government's post-market monitoring program. The program aims to ensure the continued safe, cost-effective and quality use of medicines listed on the Pharmaceutical Benefits Scheme (PBS). The purpose of this Review was to consider the comparative clinical effectiveness and cost-effectiveness of PBS listed ezetimibe, in the context of the latest available evidence and best clinical practice.

Under the Post-market review framework, the Pharmaceutical Benefits Advisory Committee (PBAC) considers the post-market review report, stakeholder comments and sub-committee advice before making recommendations. The PBAC minutes and the final report will be published on the PBS website. Recommendations and options for implementation are provided to the Minister for Health for consideration where they impact on the PBS.

### 1.1 Terms of Reference

The PMR of ezetimibe addressed the following three terms of reference:

1. Review current utilisation of Pharmaceutical Benefits Scheme (PBS) - listed ezetimibe and ezetimibe combination products. Any review will consider additional data sources that may inform the current utilisation of ezetimibe.
2. Review recent clinical guidelines for the treatment of hypercholesterolaemia and compare this to how ezetimibe is currently used on the PBS.
3. Collate and evaluate any recent clinical studies of ezetimibe that report on long-term patient relevant outcomes, and use this data to review the cost-effectiveness of ezetimibe.

### 1.2 Background

Following consideration of submissions for combinations of ezetimibe plus atorvastatin (November 2013) and ezetimibe plus rosuvastatin (July 2014), the PBAC expressed concern that the listing of ezetimibe/statin fixed dose combination (FDC) products may direct use away from optimal dosing with statin monotherapy. At that time, there were no long term patient relevant outcome data available for ezetimibe. In October 2014, the DUSC considered an analysis of PBS utilisation of subsidised ezetimibe/simvastatin products. The analysis found that:

- The number of new patients initiating ezetimibe was steady, with approximately 38,000 new patients each year. The number of prevalent patients on ezetimibe was increasing over time, and the majority of patient use was in ezetimibe/statin combinations.
- The listings of the 10-10 mg and 10-20 mg FDCs of ezetimibe plus simvastatin were expected to replace the concomitant use of ezetimibe and simvastatin. This was not the case and in the twelve months after listing, use of these FDCs was higher than expected and did not substitute concomitant use of ezetimibe and simvastatin as predicted.

The PBAC subsequently recommended a post-market review of ezetimibe on 14 August 2015.

## 2. KEY FINDINGS OF THE REVIEW

### 2.1 Term of Reference 1: Review current utilisation of Pharmaceutical Benefits Scheme (PBS) listed ezetimibe and ezetimibe combination products.

An analysis of unit record level PBS data was conducted to identify people first dispensed ezetimibe alone or in combination with a statin or other non-statin lipid lowering therapy (LLT) during the period April 2014 to March 2015. The details of this analysis are provided in Appendix E of the Review report. This analysis was conducted in a sample of the complete PBS dataset (including under co-payment prescriptions) for all lipid lowering medicines (ATC C10) dispensed between April 2012 and March 2016. The aim of this study was to answer the following research question:

> "*Is ezetimibe being prescribed on the PBS in accordance with the PBS restrictions for ezetimibe, which require titration of statins to maximally tolerated doses before initiation of treatment with ezetimibe?*"

The study identified that 45,465 people initiated ezetimibe in the 2014-15 twelve month period. The analysis found that 6,938 (or 15%, subsequently referred to as Cohort 1) people initiating ezetimibe had no LLT dispensed in the prior 24 months. The remaining 38,707 (or 85%, subsequently referred to as Cohort 2) had at least one LLT lipid lowering prescription dispensed in the 24 months prior to ezetimibe initiation.

The March 2017 utilisation analysis categorised all new users of ezetimibe according to both pre- and post-use of statins and other LLT. For those patients initiating ezetimibe:

- 46% appeared to have initiated ezetimibe in accordance with the PBS restriction
- 18.4% appeared to have initiated ezetimibe in a manner that was not consistent with the PBS restriction,and
- 34.8% initiated ezetimibe and compliance with the PBS restriction was unknown.

### 2.2 Term of Reference 2- Review recent clinical guidelines for the treatment of hypercholesterolaemia

A systematic literature review of the most recent Australian and international clinical treatment guidelines identified 11 treatment guidelines for management of metabolic lipid disorders to prevent cardiovascular outcomes. The most recent revisions of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) task force 2016 guidelines and 2016 American College of Cardiology (ACC) Clinical Expert Consensus decision pathway were included. The details of this report are provided in Appendix G.

The literature review found the approach to treatment to prevent cardiovascular events is similar across the identified guidelines. All guidelines emphasised the use of LLT as a key intervention in the approach to cardiovascular risk reduction.

The variation between Australian and international guidelines reflects differences in absolute risk thresholds and the available pharmacotherapy in each country.

All guidelines recommend that diet and exercise should be the first management step for patients with an elevated cardiovascular risk. Most guidelines list statins as the first pharmacotherapy of choice in patients who have increased risk of cardiovascular disease. When patients require additional reduction of low density lipoprotein-cholesterol (LDL-C), clinical guidelines then recommend prescribing ezetimibe. The positioning of ezetimibe as second line therapy reflects the greater body of evidence on clinical outcomes supporting statin use and the greater percentage reduction of LDL-C achieved with statin monotherapy compared to ezetimibe monotherapy.

Generally, statins are well tolerated medicines. Reports indicate that the proportion of people with a true contraindication to statins is very small. The size of the intolerant and/or contraindicated population in Australia is not able to be quantified with currently available data. An overall figure of 5-10% is considered reasonable based on literature reports. Stakeholder input and literature reviews indicate that statin associated muscle symptoms are more common than true contraindications, but that there appears to be a substantial nocebo effect, which may have been fuelled by adverse media coverage, e.g. the Catalyst program (ABC, October 2013). Strategies for managing statin intolerance include prescribing a different statin, taking a treatment break and then rechallenging, or reducing the dose of statin.

For most patients, access to PBS subsidised ezetimibe requires a trial of statin monotherapy. The General Statement for Lipid Lowering Drugs (GSLLD) is used to determine patient eligibility for PBS-subsidised lipid lowering pharmacotherapy (i.e. statins, fenofibrate, gemfibrozil) and therefore access to PBS-subsidised ezetimibe. There are minor differences between the eligibility of patients for PBS-subsidised pharmacotherapy determined through the GSLLD and the Australian clinical treatment guidelines.

A search of recently published literature found sub-group analyses of the IMPROVE-IT study which suggest that significant benefit of ezetimibe is restricted to those patients with high risk in a secondary prevention population. The Bohula et al[1] (2017) analysis defined subgroups of participants according to the level of atherothrombotic risk. Those who gained significant benefit from ezetimibe/statin therapy had three or more additional cardiovascular risk factors. Patients with prior coronary artery bypass surgery (CABG) achieved an absolute risk reduction of 8.8% compared to 1.3% for those without prior CABG. Low risk patients (nil to one risk factor) showed no benefit from the addition of ezetimibe.

[1] Bohula et al: Atherothrombotic Risk Stratification and Ezetimibe for Secondary Prevention *JACC* Vol.69,No.8 2017.

## 2.3 Term of Reference 3- Collate and evaluate any recent clinical studies of ezetimibe that report on long-term patient relevant outcomes, and use this data to review the cost-effectiveness of ezetimibe

*Clinical Studies*

The literature search sought to identify recent clinical studies of ezetimibe reporting on relevant long term patient outcomes (survival, quality–adjusted survival, fatal and non-fatal cardiovascular events) or superior surrogate outcomes (total cholesterol, LDL-C and HDL-c). No trials were identified that reported on patient relevant outcomes for ezetimibe monotherapy.

There was insufficient clinical trial evidence in addition to that previously considered by the PBAC to assess long term patient outcomes associated with adding ezetimibe to the maximum tolerated dose of a statin, compared to placebo plus maximum tolerated dose of a statin.

The literature review identified one study of long-term patient related outcomes of ezetimibe added to statin therapy. This study was applicable to only a subset of the Australian population eligible for PBS-subsidised ezetimibe. The IMPROVE-IT[2] study, conducted in the secondary prevention population, assessed long-term patient outcomes associated with the addition of ezetimibe 10mg to simvastatin 40mg versus placebo plus simvastatin 40mg. There was no statin up-titration to maximally tolerated doses or switch to statin of a higher potency as required by the current PBS restriction for ezetimibe. The trial population did not meet the PBS eligibility criteria for subsidised prescription of ezetimibe for a number of reasons.

The clinical outcomes of the IMPROVE-IT trial support the role of ezetimibe as a non-statin LLT option for the reduction of cardiovascular risk when added to statin therapy. Outcomes of the IMPROVE-IT trial confirm that the absolute reduction in LDL-C is a valid surrogate for reduction of the relative risk of major vascular events. The reduction in cardiovascular event rate in the study population who received ezetimibe and statin was as predicted by the known relationship between absolute reduction in LDL-C and the relative risk reduction. On the basis of IMPROVE-IT outcomes, long-term use of ezetimibe appears to be safe.

For ezetimibe monotherapy, results of the meta-analyses of eight randomised controlled trials (nine for HDL-C results) reported in the systematic review by Pandor[3]; indicate that ezetimibe reduced LDL-C concentrations by approximately 18% from baseline compared with placebo. By comparison, statins, depending on dose and potency, reduce LDL-C by at least 30-50% from baseline. None of the trials included in the meta-analyses enrolled patients with confirmed statin intolerance or contraindication to statin therapy. Ezetimibe monotherapy appeared to be well tolerated with a safety profile similar to placebo.

[2] Cannon CP, Blazing MA, Giugliano RP et al Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes *N Engl J Med* 2015; 372:2387-2397 June 18, 2015DOI: 10.1056/NEJMoa1410489

[3] Pandor, A., Ara, R. M., Tumur, I., Wilkinson, A. J., Paisley, S., Duenas, A., Durrington, P. N. and Chilcott, J. (2009), Ezetimibe monotherapy for cholesterol lowering in 2,722 people: systematic review and meta-analysis of randomized controlled trials. Journal of Internal Medicine, 265: 568–580. doi:10.1111/j.1365-2796.2008.02062.x

The greater absolute reduction in LDL-C (and cardiovascular risk reduction) achieved by most strengths and types of statins support statins as first line therapy for hypercholesterolaemia. The magnitude of the absolute reduction in LDL-C through the addition of ezetimibe is dependent on the LDL-C concentration following treatment with maximum tolerated doses of statin. Ezetimibe will provide benefits not achieved otherwise for patients who are contra-indicated to, or cannot tolerate, higher statin doses.

*Cost-effectiveness*

The cost-effectiveness of ezetimibe in combination with statin, versus maximally tolerated statin monotherapy, remains uncertain given the limited clinical evidence on long-term patient relevant outcomes and lack of direct applicability of the IMPROVE-IT study population to the PBS population.

The results of the Bohula et al[4] analysis of IMPROVE-IT showed significant benefit of ezetimibe/statin combination therapy only in those patients with very high cardiovascular risk. These data support use of ezetimibe in second line therapy following optimal use of statins and in those patients with very high risk.

*Review of the economic modelling of ezetimibe*

The sponsor of ezetimibe submitted a modelled economic evaluation to the Post-market Review. The economic evaluation assessed the cost-effectiveness of adding ezetimibe to background treatment with a statin (simvastatin 40 mg) in the patient population eligible for PBS subsidised ezetimibe therapy. The model used the same Markov structure and transition probabilities as was previously considered by the PBAC in seven economic models for ezetimibe between December 2003 and March 2012. All previous concerns highlighted by the PBAC apply to this model.

Changes in total cholesterol (TC) and high density lipoprotein-cholesterol (HDL-C) ratio (TC: HDL-C) were used to predict coronary heart disease events and mortality. The Incremental Cost-Effectiveness Ratio (ICER) is sensitive to the estimates of clinical efficacy in terms of TC: HDL ratio provided in the sponsor's submission and those derived during the post-market review. Alternative efficacy estimates were obtained for a sensitivity analysis from the meta-analysis of trials that enrolled primary, secondary or mixed prevention populations, which more closely matches the PBS eligible population.

[redacted]

[4] Bohula et al :Atherothrombotic Risk Stratification and Ezetimibe for Secondary Prevention *JACC* Vol.69,No.8 2017.

The base case ICER presented in the sponsor's submission was thus considered uncertain. This is also because the approach used for extrapolating the benefits beyond the period of the trial follow-up was likely to have overestimated the incremental long-term benefits associated with a combination of ezetimibe and a statin.

The evaluation concluded that an economic model based on the results of the IMPROVE-IT trial would not provide a reasonable estimate of the cost-effectiveness of current ezetimibe use on the PBS due to applicability issues. The cost-effectiveness of ezetimibe in combination with statin versus maximally tolerated statin monotherapy remains uncertain due to current utilisation evidence that shows people were not being optimally titrated with statins prior to commencing ezetimibe.

In considering the cost-effectiveness of ezetimibe, a weighted comparison compared to multiple comparators, including up-titration of statin dose, switching to higher potency statins, cholestyramine and placebo may be one way to estimate the cost-effectiveness of ezetimibe in current practice.

## 3. STAKEHOLDER COMMENTS

Extensive stakeholder consultation was undertaken. Stakeholder submissions addressing the Terms of Reference and the stakeholder forum summary were published on the Post-market Review of ezetimibe website. Submissions addressing the draft report are included as an appendix to the final report. The PBAC noted and welcomed the input from individuals, health care professionals, industry and organisations. Key comments included:

### 3.1 Term of Reference 1

- Prescribers and patients place significant value on ezetimibe's ability to lower LDL-C and event risk without increasing the likelihood of adverse effects associated with higher statin doses.
- Prescribers use combination treatment in high LDL-C and high clinical risk situations when it is considered that adequate LDL-C lowering with statin monotherpy alone may not be achieved.
- Access to non-statin therapies is important for patients who are unable to achieve treatment targets, or for those who are unable to tolerate statins.
- Ezetimibe is the predominant non-statin therapy reflecting the focus on LDL-C as the primary treatment target.
- Only a small proportion of patients are truly intolerant to statins. For example, clinical trials show that approximately 1-5% of patients are intolerant, with possibly up to 10% of patients partially intolerant. However, up to 20% of patients report muscle symptoms.
- Negative publicity from the Catalyst program (ABC, October 2013) has had a significant impact on patient perceptions and preferences and may impact on the proportion of patients that start ezetimibe without having first taken a statin.
- There may be clinically valid reasons for patients commencing ezetimibe without trialling maximal doses of statins.

- Support for measures to improve prescriber, pharmacist and patient education and to promote programs that support patients being compliant to therapy.

### 3.2 Term of Reference 2

- LDL-C is increasingly recognised as the primary lipid treatment target in patients with high cardiovascular risk. LDL-C treatment targets to be achieved through pharmacotherapy have become progressively lower over time.
- There may be differences between approaches to treatment in hospital and the community. The current guidelines are generally consistent with the General Statement for lipid lowering drugs subsidised on the PBS.
- Some overseas guidelines, namely those from the American College of Cardiology and the American Heart Association, have been recently revised to recommend the additional use of non-statin cholesterol-lowering medicines such as ezetimibe to high risk patients who do not reach targets with statins alone.
- There is more confidence in the greater LDL-C lowering effect of statins than ezetimibe
- Ezetimibe as a second line therapy may be justified due to the significant reductions in the price of statins, resulting in ezetimibe's price, relative to statin therapy, being higher than at the time of initial listing.
- The PBS General Statement is complicated and revision may be beneficial.

### 3.3 Term of Reference 3

- If ezetimibe utilisation is found to be consistent with the intent of the PBS restriction and within local clinical guidelines, it is unnecessary to review the cost-effectiveness of ezetimibe.
- There have been no other changes in the intervening period in terms of PBS listings, local treatment guidelines or choice of comparator that would warrant reconsideration of the cost-effectiveness of ezetimibe.
- New evidence from the IMPROVE-IT study has confirmed the benefit of adding ezetimibe to statins.
- The IMPROVE-IT result has been described as proof that LDL-C is a causal factor of cardiovascular disease and reducing LDL-C reduces risk of cardiovascular disease.
- It is important to consider the depth of evidence and applicability of studies to the Australian context
- The experiences of failed studies (studies that did not demonstrate outcomes) is also relevant to this Review.
- Key findings of the IMPROVE-IT study were stated to be validation of LDL-C as a surrogate, However, the morbidity benefit of adding ezetimibe to statin has been shown in high risk populations only (secondary population) and there was no gain in mortality in the same high risk population.
- With regard to cost-effectiveness, the addition of a second comparator, higher doses of statin, was felt to be inconsistent with the position of ezetimibe as a second-line agent.

- With regard to the duration of the economic model, a lifetime duration was consistent with the current statements for chronic diseases in the PBAC Guidelines for submissions to list medicines on the PBS.

## 4. PBAC CONSIDERATION AND ADVICE TO THE MINISTER FOR HEALTH

Overall, the PBAC accepted the key findings presented in the ezetimibe Review Report. The PBAC considered stakeholder submissions to the Review, the Sponsor's Pre PBAC response and ESC and DUSC advice in addition to the Report. The PBAC noted the evidence on the long- term patient outcomes was limited to one study, IMPROVE-IT, and that the eligible patient population in this study was not representative of the current PBS population eligible for subsidised ezetimibe. The PBAC acknowledged the stakeholder comments and recognised the challenges in accurately determining the extent of statin intolerance in the Australian population. The PBAC was concerned with the extent of use of ezetimibe outside the PBS restriction and considered whether a price reduction was necessary to restore cost-effectiveness. The PBAC agreed that an Authority Required (Streamlined) listing was most appropriate to maintain ezetimibe's place as second line therapy, consistent with clinical guidelines and to direct use to the high-risk population that would derive most benefit from therapy.

The PBAC considered the following questions in formulating its recommendations and in providing advice to the Minister.

### 4.1 Term of Reference 1

*4.1.1 Whether the PBAC accepts the DUSC advice findings of the utilisation report (March 2017 Analysis) that indicate the estimate of ezetimibe use that is not consistent with the PBS restriction would fall somewhere in the range of 18.4% - 53.2%. The DUSC estimated approximately half of those in whom compliance is unknown (34.8%) may not be optimally treated with statin before initiating ezetimibe, resulting in an estimate of approximately 35.8% (18.4% + 17.4%) of all ezetimibe use being outside the PBS restriction.*

The PBAC accepted the findings of the March 2017 utilisation analysis which found that for the total population initiating ezetimibe (between 1 April 2014 to 31 March 2015), 18.4% of patients were treated in a manner that was not in accordance with the PBS restriction for ezetimibe and 34.8% of patients were treated in a manner in which accordance with the PBS restriction for ezetimibe was unknown.

The PBAC considered the estimate (18.4%-53.2%) of people receiving ezetimibe outside the PBS restriction for ezetimibe is substantial, and important given that this subsidised utilisation may not be cost-effective. The PBAC noted the sponsor's justification that a substantial proportion of patients with 'unknown compliance' are likely to be within the ezetimibe PBS restriction (PSCR p2-3). However, the PBAC did not accept the estimates provided by the sponsor. The PBAC accepted the DUSC's estimate that approximately half of the 'unknown compliance' group (34.8%) may not be optimally treated with statin as required by the PBS restriction prior to initiating ezetimibe.

Based on the analysis, the PBAC considered the estimate of ezetimibe use outside the restriction would be at least 18.4% and that the DUSC estimate of approximately 35.8 % (18.4% + 17.4%) was reasonable and more likely.

The sponsor's pre-PBAC response (p.3) maintained that use outside of the restriction is limited to 10% when a longer "look back" period of eight years is used and argued that a two year "look back" period is too short, given the chronic nature of treatment for high cholesterol. The PBAC agreed with the DUSC advice that, while longer "look back" periods would identify more people with prior use of statins, there was no evidence from PBS data to indicate whether those patients were intolerant or non-compliant. In addition, patients in this group who initiate ezetimibe and statin combinations cannot therefore be considered intolerant or contra-indicated to statins.

Stakeholder input suggests that ezetimibe is often prescribed before statin up-titration in the belief that this may reduce potential statin adverse effects, rather than for reasons of intolerance to higher dose/potency statin. The DUSC considered there was no safety basis for the approach of adding a less effective medicine to sub-optimal doses of a more effective therapy. The PBAC agreed with the ESC that patient preference for ezetimibe over statins is not an adequate justification for using ezetimibe without first trialing a statin and that use in this manner, or where statins are not optimally titrated first, would not be cost-effective.

The PBAC acknowledged that widespread community concern and misinformation persists around the side effects and harms associated with statins. Prescribers report patients may either refuse to take statins or not take statin therapy as prescribed and therefore may fail to achieve target LDL-C concentrations. Prescribers may also maintain patients on a combination of lower dose statin and ezetimibe rather than trial higher dose or more potent statins because the patients are at LDL-C treatment targets and not experiencing adverse effects. Whilst this approach is clinically effective, cost-effectiveness has not been demonstrated.

***PBAC Advice: The PBAC considered the estimate of ezetimibe use outside the restriction would be at least 18.4% and agreed that the DUSC estimate of approximately 35.8% was reasonable.***

### 4.2 Term of Reference 2

*4.2.1 Whether the PBAC may wish to request that future education programs reinforce and promote use of statins first line at the maximum tolerated dose for optimal LDL-C reduction and management of cardiovascular risk?*

The PBAC considered the Post-market Review presents an opportunity to promote optimal LDL-C reduction and improve management of cardiovascular risk in the community. The PBAC recommended that statins be promoted as first line lipid lowering therapy, consistent with all clinical guidelines for the management of hypercholesterolaemia and the large body of evidence supporting statin use. Ezetimibe (10 mg dose daily) produces an 18% reduction in base-line LDL-C concentration. Most strengths and types of statins achieve a greater absolute reduction in LDL-C

compared to ezetimibe monotherapy. The 2014 NICE Guidance Development Group consensus placed statins into three different intensity categories according to the percentage reduction in LDL-C concentration. The reduction in LDL-C concentration between statins of differing doses and intensities is shown in Table 1 below.

**Table 1: Grouping of statins by intensity category used in the 2014 NICE Guidance**

| | Reduction in low density lipoprotein cholesterol | | | | |
|---|---|---|---|---|---|
| **Dose (mg/day)** | **5** | **10** | **20** | **40** | **80** |
| **fluvastatin** | | - | 21%[1] | 27%[1] | 33%[2] |
| **pravastatin** | | 20%[1] | 24%[1] | 29%[1] | - |
| **simvastatin** | | 27%[1] | 32%[2] | 37%[2] | 42%[3,4] |
| **atorvastatin** | | 37%[2] | 43%[3] | 49%[3] | 55%[3] |
| **rosuvastatin** | 38%[2] | 43%[3] | 48%[3] | 53%[3] | - |

Source Table 1, Appendix A; 2014 NICE Guidance/cg181. Reproduced from Review of Clinical Guidelines-CPHR Deakin University, p50.

[1]20%-30%: low intensity, [2]31%-40%: medium intensity, [3]Above 40%: high intensity, [4]Advice from Medicines and Healthcare products Regulatory Agency (MHRA): there is an increased risk of myopathy associated with high dose (80 mg simvastatin)

Clinical guidelines recommend the addition of ezetimibe when patients require additional reduction of LDL-C or where a patient is intolerant of, or has a contraindication to, statin therapy. Unless contraindicated, a trial of maximal tolerated doses of statins prior to adding ezetimibe is recommended because this approach achieves the greatest absolute reduction in LDL-C and therefore greater reduction in cardiovascular risk. The PBAC noted trialing higher dose statins prior to adding ezetimibe is the basis for the current PBS restriction and cost-effective use of ezetimibe.

The PBAC considered the PBS data analysis and stakeholder input suggests ezetimibe is often prescribed before statin up-titration to avoid perceived statin side effects. There is dispute around the size of the statin intolerant or contraindicated Australian population. The DUSC highlighted the difficulty of diagnosing true statin associated muscle symptoms (SAMS) with recent literature suggesting a nocebo effect. In randomized blinded controlled trials of statins, adverse events are rare compared with observational studies in which adverse events are reported by up to 20% of patients[5]. Ezetimibe is also associated with myalgia. The PBAC noted a recent study[6], where patients reporting SAMS were subsequently randomized to ezetimibe or evolocumab. Muscle symptoms were reported in 28.8% of ezetimibe-treated patients.

The PBAC agreed with the DUSC that the March 2017 utilisation analysis was not designed to address issues of adherence and persistence in the broader Australian population taking LLT. However, the PBAC recommended that prescriber education promote the importance of adherence and persistence with LLT for optimal management of cardiovascular risk. The PBAC acknowledged consumers may still be influenced by adverse media publicity for statins from the

[5] www.thelancet.com Published online May 2 2017 http://dx.doi.org/10.1016/s0140-6736(17)31075-9
[6] JAMA. 2016 Apr 19;315(15):1580-90. doi: 10.1001/jama.2016.3608.

ABC's Catalyst program (2013). The PBAC recommended promotion of strategies to clinicians to manage perceived and real stain intolerance including statin dose reduction, prescribing a different statin, taking treatment breaks and initiating a statin re-challenge prior to prescribing ezetimibe or another LLT. This education will be critical to cost-effective PBS expenditure on LLTs as new high cost LLTs seek PBS listing in the future.

The PBAC noted the sponsor maintains (Pre-PBAC response, p3) that statin intolerance is a major concern for clinicians and patients and supports education that assists in the effective management of high cholesterol.

***PBAC Advice: The PBAC recommended that Quality Use of Medicines initiatives such as prescriber education programmes be undertaken to promote the use of statins first line, promote the use of maximal tolerated doses of statins prior to adding ezetimibe, reinforce the importance of adherence and persistence to lipid lowering therapy and to communicate strategies for the management of actual and perceived statin intolerance.***

*4.2.2 Whether the PBAC agrees to the removal of the General Statement for Lipid Lowering Drugs (GSLLD) from the PBS restriction for statins, fenofibrate and gemfibrozil?*

The PBAC agreed that the GSLLD no longer reflects current prescribing or newer updated clinical practice guidelines for LLTs. PBS subsidised access to ezetimibe for most patients requires a trial of statin therapy. Removal of the GSLLD from the statin, gemfibrozil and fenofibrate restrictions would, in turn, require revision of the ezetimibe PBS restriction.

The GSLLD is based on absolute risk of a cardiovascular event over a 15 year period. The GSLLD does not account for all risk factors such as chronic kidney disease and age. Commencing treatment with a LLT is dependent on consideration of individual risk factors. Since the inception of the GSLLD, clinical management of cardiovascular risk has been further refined with a greater emphasis in recent guidelines on overall risk assessment and management rather than using specific numerical targets for each identifiable risk factor.

The PBAC noted there are small differences between the GSLLD and the Australian clinical treatment guidelines for hypercholesterolaemia. The PBAC acknowledged feedback from the stakeholder forum that the General Statement is complex and PBS restrictions do not fully reflect prescribing practice that is consistent with Australian guidelines. The PBAC agreed with its subcommittees that the removal of the GSLLD is is unlikely to significantly impact utilisation of LLTs and will remove unnecessary complexity from prescribing PBS subsidised LLT. The PBAC also noted the sponsor's support for removal of the GSLLD (Pre-PBAC response, p3).

***PBAC Advice: The PBAC recommended the requirement to meet the clinical criteria set out in the GSLLD be removed from the PBS restrictions for all statins, gemfibrozil and fenofibrate. As a result the restriction for ezetimibe will also require alteration to accommodate this change.***

*4.2.3 Whether the PBAC agrees with the Reference Group recommendation to consider derestriction of statins from Restricted Benefit to unrestricted benefit?*

The PBAC recommends removal of the current Restricted Benefit level of restriction for statins. The PBAC considered that PBS-listing statins as unrestricted benefits would allow statin prescribing to remain consistent with current evidence as reflected in the current Australian Guidelines. In making the recommendation, the PBAC noted the role of PBS restrictions in supporting good clinical practice and, in this instance, not being perceived to be a barrier to care that is consistent with current clinical guidelines.

The PBAC acknowledged the large volume of quality evidence that indicates lowering LDL-C with statins translates to a reduction in risk of cardiovascular events in both primary and secondary prevention populations, which is the PBS subsidised population. The PBAC noted that statin prices had been substantially reduced through PBS Statutory Pricing Policy over the last decade.

The PBAC noted that Australia's statin use is one of the highest of all OECD countries (Health at a Glance, OECD Health Statistics 2015). The PBAC agreed with the DUSC that the statin market is stable and mature and that relaxation of the PBS restriction to 'unrestricted' is very unlikely to substantially impact the utilisation of statins. Growth in the statin market may even be desirable, as it is likely to reflect identification and treatment of higher risk individuals who are currently not being treated, or who are being treated with other LLT that are less cost-effective than appropriate statin usage.

***PBAC Advice: The PBAC recommended the Restricted Benefit PBS restriction for statins be amended to unrestricted benefit.***

*4.2.4 Whether the PBAC agrees with the Reference Group advice that ezetimibe remain second line therapy, compatible with clinical guidelines, via an Authority Required 'Streamlined' PBS listing?*

The PBAC considered that, while the statin market is mature in comparison to when ezetimibe was first listed, the ezetimibe market could not be considered stable as approximately 45,000 patients initiate ezetimibe therapy annually. The PBAC noted the DUSC advice that the prevalent population is increasing and that use of ezetimibe is predominantly in fixed dose combinations with statins.

The PBAC considered that a telephone Authority Required listing may be more appropriate to restrict PBS subsidised cost-effective use of ezetimibe to the high risk population, but was cognisant of the large number of patients taking ezetimibe and the administrative burden that this change in restriction type would impose on prescribers, patients and the Department of Human Services. The PBAC considered that maintenance of the PBS Authority Required (Streamlined) level of restriction is consistent with the placement of ezetimibe by clinical guidelines as second–line

therapy following statin treatment, either as add on or as monotherapy for statin intolerance/contraindication.

The PBAC recommended that ezetimibe should remain Authority Required (Streamlined) and therefore second line to maximally tolerated doses of statins, given the limited clinical evidence available for ezetimibe on patient relevant outcomes, and the superiority of statins in LDL-C lowering and reduction in patient relevant outcomes. Should cost-effectiveness not be restored through other means, for example a price reduction to account for use outside the PBS restriction, then the PBAC considered increasing the level of restriction from Authority Required (Streamlined) to telephone Authority Required may be appropriate.

***PBAC Advice: The PBAC recommended the PBS restriction for ezetimibe should remain Authority Required (Streamlined). The PBAC recommended an increase in the level of restriction to telephone 'Authority Required' should cost-effectiveness not be restored. This would include a price reduction accounting for non-cost-effective use of ezetimibe.***

*4.2.5 Whether the PBAC agrees with the suggested revised restriction for ezetimibe?*

The PBAC acknowledged the length and complexity of current ezetimibe and ezetimibe plus statin combination product PBS restrictions. The PBAC agreed in principle to the proposed revised ezetimibe restrictions as detailed in the Review Report (abbreviated version Box 1, p.14).

The PBAC noted that consistent with the current ezetimibe restriction, the proposed restriction covers access to PBS subsidised ezetimibe to those patients with very high risk and:

- inadequate control of cholesterol levels with statin therapy, or,
- statin contraindicated, or
- reduction in statin dose due to an adverse event,or
- withdrawal of statin therapy due to an adverse event.

The PBAC also noted the proposed restriction facilitates access to PBS subsidised ezetimibe for those patients with inadequate control of cholesterol levels with statin therapy and who have an absolute risk of a cardiovascular event greater than 15% over 5 years. The PBAC agreed with the ESC that risk algorithms do not incorporate all cardiovascular risk factors, that the majority of calculators are limited to assessing risk at 5 or 10 years rather than lifetime risk and that the risk calculators can be less accurate in certain populations, e.g. younger age groups.

The PBAC agreed with the DUSC that the 'treatment must be in conjunction with diet and exercise' criterion should be retained. Ezetimibe's mechanism of action inhibits the intestinal absorption of cholesterol and related plant sterols. Advice to reduce dietary fat intake and increase exercise may be complementary to treatment with ezetimibe.

The PBAC agreed that the revised restriction for ezetimibe refer to inadequate control with a statin where serum LDL-C > 2.5mmol/L, instead of total cholesterol of > 4mmol/L.

The PBAC considered that implementation of the revised restriction presents an educational Quality Use of Medicines opportunity to promote the importance of absolute risk reduction in the approach to cardiovascular disease management.

***PBAC Advice: The PBAC recommended the Authority Required (Streamlined) restriction be revised as detailed in the Review Report. Implementation of the revised restriction should be utilised as an educational opportunity. The PBAC also recommended the revised PBS restriction criteria for ezetimibe:***

- ***retain the statement 'treatment must be in conjunction with diet and exercise' and***
- ***refer to inadequate control with a statin where serum LDL-C > 2.5mmol/L rather than total cholesterol of > 4mmol/L.***

### 4.3 Term of Reference 3

*4.3.1 Does the PBAC agree that the current use of ezetimibe and the applicability of the IMPROVE-IT trial means the cost-effectiveness of ezetimibe in combination with statin versus statin monotherapy is uncertain?*

The PBAC agreed that there is ongoing uncertainty regarding the cost effectiveness of PBS use of ezetimibe. The PBAC accepted the DUSC estimate that approximately 35.8% of PBS subsidised ezetimibe use is outside the PBS restrictions. The PBAC also noted that the comparators for ezetimibe do not appropriately include up-titrating the statin dose or switching to a higher potency statin. This is the LLT most likely to be used as an alternative by patients using ezetimibe outside the restriction. It is noted that the sponsor argued that placebo and non-statin LLT should be the comparators for ezetimibe, rather than up-titrated dose of statin or use of a higher potency statin.

The IMPROVE-IT trial population is not directly applicable to the PBS population. The trial population did not meet the PBS eligibility criteria for subsidised prescription of ezetimibe for a number of reasons.

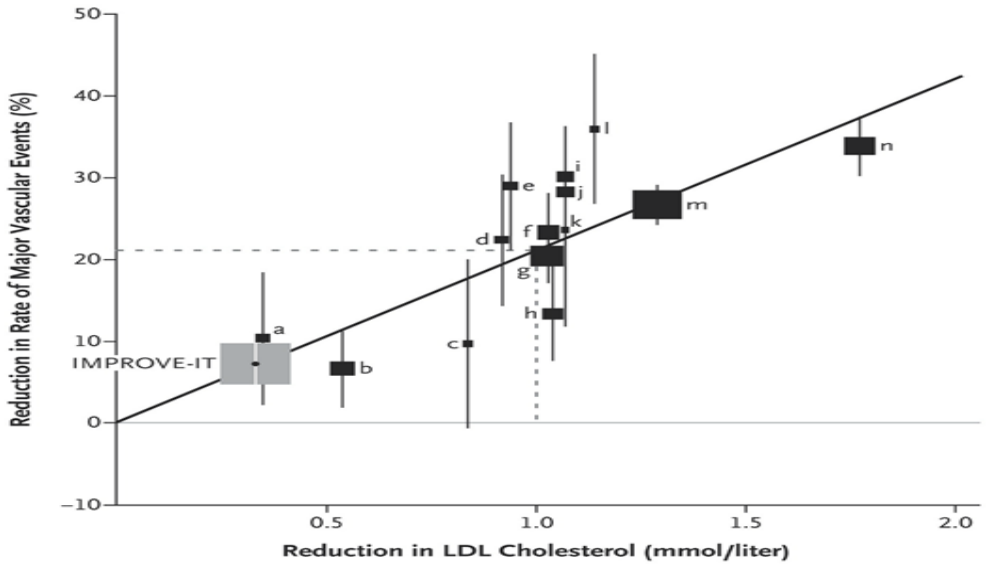
The PBAC also considered the findings of the recent Bohula et al (2017) re-analysis of the IMPROVE-IT trial where patients with three or more additional cardiovascular risk factors showed a significant benefit from ezetimibe plus statin therapy over statin monotherapy. Low risk patients (nil to one risk factor) showed no benefit from the addition of ezetimibe. Recent literature also suggests that significant benefit from ezetimibe is restricted to those with high risk of cardiovascular events in a secondary prevention population. This underlines the importance of restricting use of ezetimibe to second line therapy use after optimal use statins and in patients with very high risk to maintain cost-effectiveness.

*4.3.2 Whether the IMPROVE-IT trial adequately supports the hypothesis that a reduction in LDL-C is a valid surrogate outcome for reduction in overall cardiovascular risk? A risk reduction in a primary composite endpoint was demonstrated (cardiovascular death, major coronary event or non-fatal stroke) with no significant overall effect on mortality alone.*

The PBAC agreed that the IMPROVE-IT trial supports the hypothesis that a reduction in LDL-C is a valid surrogate outcome for a reduction in overall cardiovascular risk. IMROVE-IT demonstrated a risk reduction in a primary composite endpoint (cardiovascular death, major coronary event or non-fatal stroke). There was no significant effect on overall mortality alone, noting that the trial was not powered to detect a mortality benefit.

The IMPROVE-IT trial confirms that ezetimibe lowers risk of cardiovascular events to an extent predicted by the relationship between absolute LDL reduction and CV risk obtained from previous studies with other lipid-lowering agents. These results confirm that reduction in LDL-C appeared to be a valid surrogate for a reduction in rate of major vascular events (see Figure 1 below). The risk reduction observed in the IMPROVE IT trial was also consistent with the absolute reduction in LDL-C predicted by the Cholesterol Treatment Trialists (CTT) statin derived regression line (see Figure 1 below). A 1.0 mmol/L reduction in LDL-C reduces cardiovascular risk by around 22%. The relative risk reduction for LDL-C lowering is the same for both primary and secondary prevention populations, whereas the absolute risk reduction changes dependent on background risk.

**Figure 1: Plot of the IMPROVE-IT Trial Data and Statin Trials for Change in Low-Density Lipoprotein (LDL) Cholesterol versus Clinical Benefit.**




Source: Cannon et al. (2015). Ezetimibe added to statin therapy after acute coronary syndromes. The New England Journal of Medicine, 372:2387-2397

*4.3.3 Whether the PBAC agrees that in considering the cost-effectiveness of ezetimibe, the comparators include:*

- *placebo/non statin lipid lowering therapy (LLT) for those patients contraindicated or intolerant of statins and*
- *up-titration of statin to maximum tolerated dose/switching to a higher potency statin?*

When ezetimibe was first considered for PBS listing in 2003, the PBAC accepted that the main comparator was cholestyramine for patients intolerant to, or with contraindications to, statins; and placebo for patients who were on maximum tolerated doses of statins where cholesterol was not adequately controlled.

The sponsor's Pre-Sub-Committee Response (January 2017 PSCR, p2-3) maintained that the comparators previously accepted by the PBAC are the most appropriate. The ESC noted the January 2017 PSCR (p1) states 'prescribers and patients place significant value on ezetimibe's ability to lower LDL-cholesterol and event risk without increasing the likelihood of side effects associated with higher statin doses'. This statement suggests prescribers are adding ezetimibe to lower statin doses ahead of up-titrating statins. Therefore, the PBAC agreed that if this is what occurs in clinical practice, then high dose statins can be a relevant comparator for a sub-group of the population treated with ezetimibe.

The PBAC agreed with the ESC that in addition to the patient populations identified when initially considering submissions for ezetimibe, there is likely to be a proportion of patients who are not receiving maximally tolerated doses of high potency statins for reasons other than contraindication or intolerance. In these patients, up-titration of doses to a maximally tolerated dose of statin or switching to a higher potency statin is an appropriate comparator.

The PBAC also agreed with ESC that a weighted comparison compared to multiple comparators, including up-titration of statin dose, switching to higher potency statin, cholestyramine and placebo, may be one way in which to estimate the cost-effectiveness of ezetimibe in current practice.

***PBAC Advice: The PBAC recommended that in assessing the cost-effectiveness of PBS-subsidised ezetimibe in line with current PBS use, the appropriate comparators are up-titration of statin dose to maximum tolerated doses, switching to a higher potency statin, cholestyramine and placebo.***

*4.3.4 Whether the PBAC agrees the magnitude of additional LDL-C reduction from the addition of ezetimibe to a statin is likely to be comparable to the magnitude of the reduction in LDL-C from up-titrating the doses or switching to a higher potency statin and that the significantly higher price of ezetimibe is not justified in this situation?*

The PBAC noted the findings of the literature review that the particular statin used and statin dose is important in determining the relative efficacy in LDL-C reduction with ezetimibe and statins. Ezetimibe produces a mean 18% reduction in LDL-C while statins can achieve reductions in LDL-C of 30-50%. Similar reductions in LDL-C are achieved using ezetimibe plus a lower potency statin or a high dose, high potency statin alone.

The ESC considered that the magnitude of the additional LDL-C reduction from the addition of ezetimibe to a statin (0.9mmol/L) is likely to be comparable to the magnitude of the reduction in LDL-C achieved from up-titrating the dose or change to a higher potency statin (2.4mmol/L).

The PBAC considered that this supports the approach to optimise the statin dose before adding ezetimibe and that the significantly higher price of ezetimibe compared to statin would appear not to be justified in this scenario. The PBAC noted the sponsor argued (Pre-PBAC response p.4) that the comparison of LDL-C lowering of ezetimibe to statin up-titration is not relevant because statin is not a comparator to ezetimibe in the current reimbursed setting.

The PBAC also noted that a 1.0mmol/L decrease in LDL-C by statin therapy reduces cardiovascular risk by approximately 22%, and that the cost of achieving the same reduction in LDL-C is significantly higher with ezetimibe than with statins.

***PBAC Advice: The PBAC agreed the magnitude of additional LDL-C reduction from the addition of ezetimibe to a statin is likely to be comparable to the magnitude of the reduction in LDL-C from up-titrating the doses or switching to a higher potency statin. The PBAC recommended that the higher price of ezetimibe is not justified in this situation.***

*4.3.5 Does the PBAC consider a price reduction appropriate based on a proportion of use between 18.4% - 53.2% where the appropriate comparator should be higher dose statin or switching to a higher potency statin to restore the cost-effectiveness of PBS-subsidised ezetimibe?*

The PBAC acknowledged that proportion of use of PBS subsidised ezetimibe where compliance with the PBS restriction is unknown was unable to be accurately quantified with currently available data. However, the PBAC accepted the results of the March 2017 utilisation study that found the proportion of ezetimibe use outside the PBS restriction was at least 18.4%, and agreed that the DUSC estimate that a further 17.4% where restriction compliance was "unknown" (total = 35.8%) was reasonable. For this proportion of use, the most appropriate comparator would be higher dose statin or switching to a higher potency statins, and therefore the appropriate price of ezetimibe for 35.8% of the all PBS ezetimibe use should be comparable to the statin price.

The PBAC noted the sponsors comment (Pre-PBAC response p.1) that ezetimibe would come off patent in June 2018 and would be subject to statutory price cuts and the price disclosure process, which could result in the price of ezetimibe falling more quickly than statins, with an associated increase in cost-effectiveness.

***PBAC Advice: The PBAC recommended that a price reduction in the range of 18.4%-35.8% would be required to restore the cost-effectiveness of PBS-subsidised ezetimibe. The appropriate comparator for this proportion of ezetimibe use that is considered outside the PBS restriction is higher dose statin or switching to a higher potency statins.***

*4.3.6 Does the PBAC agree the base case incremental cost effectiveness ratio (ICER) is uncertain?*

The sponsor's submission to the post-market review presented a stepped analysis with the first step approximating a trial based analysis using IMPROVE-IT. The base-case modelled cost per life year gained (LYG) and cost per quality adjusted life year gained (QALYG) were $24,256 and $25,010 respectively. The stepped analysis and the additional sensitivity analysis demonstrated the ICER (cost/LYG) is sensitive to baseline population characteristics, efficacy changes [changes in TC: HDL ratio] and the time horizon.

The PBAC noted the base case ICER almost doubled across all time horizons when alternative efficacy estimates obtained from an ad-hoc meta-analysis of trials were used to model the reduction in TC: HDL ratios of

**Committee-in-confidence**

[redacted]

**End Committee-in-confidence**

A further analysis exploring the effect on the ICER at 10 year intervals up to 70 years showed that the ICERs estimated as either cost/LYG or cost/QALY remain unchanged when the time horizon extends beyond 30 years. The ESC considered that a time horizon of 30 years was appropriate but noted that extending this to 70 years did not impact the cost-effectiveness.

The sponsor (Pre PBAC response p.4 point 3.3.6) maintained that the analysis of pooled data from which the alternate efficacy estimates were derived (conducted during the evaluation) would not be acceptable in a standard PBAC submission. The sponsor argued that it is not appropriate to ignore the trials where ezetimibe is used as per the PBS restriction and claim the sensitivity results are representative of real current PBS ezetimibe use.

The PBAC agreed with the ESC advice that the modelled ICER for ezetimibe is sensitive to the alternate estimates of the efficacy of ezetimibe provided during the evaluation. The PBAC agreed that the ICER based on these estimates may be more representative of the real current PBS use of

ezetimibe and that the base case ICER presented in the submission was an underestimate, and therefore overestimated the cost-effectiveness of ezetimibe.

***PBAC Advice: The PBAC agreed that the base case ICER presented in the submission is uncertain and that the ICER based on the alternate estimates of the efficacy of ezetimibe are more representative of the current PBS use of ezetimibe.***

*4.3.7 Whether or not a new economic model based on the results of the IMPROVE-IT would provide a reasonable estimate of the cost-effectiveness of current ezetimibe use on the PBS?*

The PBAC accepted the ESC advice that the model used in the 2016 post market submission has the same Markov structure and transition probabilities as previously considered by the PBAC between December 2003 and March 2012. Changes in TC and HDL-C (TC: HDL-C ratio) were used rather than LDL-C to predict coronary heart disease (CHD) events and CHD mortality. All previous concerns and uncertainties highlighted by PBAC apply to this model. They include:

- Consistency between populations in different risk equations
- assumptions about anti-hypertensive medication, menopausal status, alcohol, smoking
- assumption of 1 CHD event per 1 year cycle
- time horizon of the model (70 years) given BEACH participants' average age of 60 years.

The sponsor maintained that the cycle length is not long in the context of the probability of events which cause a transition between health states and that the likelihood of multiple events in a single year is small. The sponsor also noted the ESC advice that a time horizon of 30 years is appropriate and that extending this to 70 years did not impact the cost-effectiveness (Pre-PBAC response p.4).

The PBAC agreed with the ESC advice that, due to applicability issues, an economic model based on the results of IMPROVE-IT would not provide a reasonable estimate of cost-effectiveness of current ezetimibe use on the PBS. There continues to be ongoing uncertainty regarding the cost-effectiveness of PBS use of ezetimibe, as the IMPROVE-IT population is not directly applicable to the PBS population and IMPROVE-IT does not reflect ezetimibe added to a maximum tolerated dose of statin.

***PBAC Advice: The PBAC did not recommend basing a new economic model on the results of the IMPROVE-IT study. Applicability issues would prevent the model from providing a reasonable estimate of the cost-effectiveness of current PBS subsidised ezetimibe use.***