

## Appendix H – Public Consultation

### Review Terms of Reference

Public consultation on the draft Review Terms of Reference was open between 16 October and 13 November 2015. To view the submissions, please go to the [Public Consultation website](#).

**Table of Submissions addressing draft Terms of Reference**

Submission	Author Name	Date Received
1	Academic/ Health professional	30/10/2015
2	Prof. Paul Nestel	5/11/2015
3	Academic/ Health professional	5/11/2015
4	Merck Sharpe & Dohme (Australia) Pty Limited	13/11/2015
5	Medicines Australia	13/11/2015
6	Kidney Health Australia	16/11/2015

Public consultation addressing the final Review Terms of Reference was open between 4 March and 22 April 2016. To view the submissions, please go to the [Public Consultation website](#).

**Table of Submissions addressing final Terms of Reference**

Submission	Author Name	Date Received
1	Council of Australian Therapeutic Advisory Groups (CATAG)	20/04/2016
2	Assoc. Prof. John Amerena	21/04/2016
3	Amgen Australia Pty Ltd	22/04/2016
4	Sanofi	22/04/2016
5	Merck Sharp & Dohme (Australia) Pty Limited	22/04/2016
6	Medicines Australia	22/04/2016

### Draft Report

The draft Report on the Post-market Review of Ezetimibe was made available for public comment from 30 January to 10 February 2017. Fourteen submissions were received, including from the sponsor, Merck Sharpe & Dohme (MSD); industry (2); individual health professionals (7); Medicines Australia; and professional peak bodies (3). Key points were included in the revised draft Report.

## Revised Draft Report

### Summary of Stakeholder Submissions

The revised draft Report was made available for public comment between 23 May and 6 June 2017. Eight submissions were received, including from the sponsor, MSD; industry (1); individual health professionals (3); Medicines Australia; and professional peak bodies (2). Stakeholder submissions were compiled for PBAC consideration. Key comments included:

#### Term of Reference 1

- There are additional factors that contribute to the 'uncertain' proportion of ezetimibe use outside PBS restriction:
  - Patients refuse statin therapy due to misinformation on the internet. Ezetimibe is the only alternative effective medicine for this group.
  - A clinical situation for adding ezetimibe to suboptimal statin doses is to avoid dose dependent statin adverse effects. For example, after inadequate reduction in LDL-C from initial therapy of 40 mg atorvastatin, options include increasing the dose to 80 mg (6% further LDL-C decrease) or adding ezetimibe (20% further decrease in LDL-C).
  - The atorvastatin-ezetimibe combination is frequently adequate and reduces the likelihood of myalgia, necessitating cessation of statin. Statin doses can be increased where response is inadequate.
- Ezetimibe use outside the prescribing restrictions is more likely 10% than up to 50%. Underutilisation is more prevalent than inappropriate use, particularly in secondary prevention and patients with familial hypercholesterolaemia.
- Many patients do not tolerate statins (up to 10% of real world patients), do not achieve current LDL targets on statin therapy, or do not want to take statins due to real/perceived side effects.
- Stakeholders confirmed that addition of ezetimibe to low dose statins occurs ahead of statin up-titration for patients at high risk of adverse events.
- Some stakeholders maintained that the utilisation analysis was not conducted over an appropriate time period prior to ezetimibe initiation.
- The report findings rely on restricting the observed prior statin period to two years. This is relevant to interpretation but may not be relevant when determining a price variation.
- The evidence should support Report recommendations adopted by the PBAC. Price reductions based on uncertain utilisation would be inappropriate.
- There was concern that the Report advises the PBAC to consider a pricing recommendation informed by a wide utilisation range, despite finding the use of ezetimibe largely consistent with PBS restrictions and clinical guidelines.

## **Term of Reference 2**

Submissions acknowledged that statins are established as first-line treatment, and broadly agreed that ezetimibe be maintained as second-line therapy, that statins be de-restricted, and that the General Statement on Lipid Lowering Drugs be removed from the PBS. There was support for an absolute approach in assessing cardiovascular risk, noting the short comings of risk calculators in certain circumstances, including:

- An inflexible risk assessment score will be confusing for prescribers in the absence of statin restrictions.
- Risk calculators are susceptible to error, with analyses finding significant numbers of patients requiring statins excluded. There may be similar outcomes for ezetimibe.
- Restricting ezetimibe to secondary and primary prevention in patients who have a greater than 15%/5 years risk, would disadvantage patients where risk calculators underestimate risk.
- Whilst there was support for inclusion of the Australian Absolute Cardiovascular Disease Risk calculator in the ezetimibe PBS restrictions, increased prescriber education would be required. A Kidney Health Australia survey of 656 General Practitioners found 32% of respondents were unable to correctly identify when and how to use the calculator.

### ***Clinical guidelines***

- Ezetimibe is well tolerated and especially effective in combination with statins as it targets one of the two main mechanisms of cholesterol absorption. It is an important therapeutic tool in subgroups of patients.
- The Kidney Disease Improving Global Outcomes Group (KDIGO) clinical practice guidelines recommend adults with chronic kidney disease (CKD) are treated with statins or ezetimibe/statin combination.
- There was support for improved access to statin-ezetimibe co-packs to improve patient compliance.
- There was also support for education initiatives to improve prescribing of lipid lowering medicines and patient compliance.
- There was agreement that LDL cholesterol is an important and treatable risk factor and the target of therapy in coronary heart disease, stroke and peripheral vascular disease patients. Statins will remain first-line therapy for the foreseeable future.
- Ezetimibe is the only currently available cholesterol absorption inhibitor and only therapy for sitosterolemia. While not as effective as statins, it is a well-tolerated and effective second-line therapy.

### ***PBS restrictions***

- There was support for the existing PBS restriction criteria for ezetimibe initiation after statin intolerance. CKD patients have a higher rate of intolerance to high-dose statin therapy.

- There was agreement that ezetimibe be restricted to second-line therapy after maximum tolerated doses of statins due to the wealth of evidence supporting statin therapy for cardiovascular (CV) risk reduction.
- There was support for the de-restriction of statins on the PBS.
- The proposed definition for 'inadequate control of hypercholesterolaemia' in ezetimibe PBS restrictions is inappropriate because:
  - guidelines target LDL cholesterol (versus total cholesterol) for reduced CV risk; and
  - major guidelines that use LDL targets set a target of <1.8 mmol/L for high risk patients, therefore defining inadequate control of hypercholesterolaemia for high risk patients at that level would be more appropriate.

### ***IMPROVE-IT study***

- Stakeholders were reassured that the CV outcomes reported from the IMPROVE-IT trial were accepted by the Review, and there was acknowledgement that ezetimibe performed as expected in lowering CV events in the IMPROVE-IT study.
- The IMPROVE-IT study is not representative of the PBS population and broad ranging risk stratification conclusions drawn from the analysis are difficult to support.
- The IMPROVE-IT study design was flawed. The placebo group had a much higher rate of up-titration of simvastatin, diminishing the apparent efficacy of ezetimibe. In effect, the trial compared simvastatin 40 mg + ezetimibe to simvastatin 40-80 mg.
- One stakeholder noted the excellent results (RRR 27%, ARR 8%, and NNT 22) in the cohort of subjects from Australia and New Zealand, contained in the IMPROVE-IT study appendix.
- Another stakeholder noted the effect of ezetimibe in the diabetes population as shown in the Bohula et al. analysis of the IMPROVE-IT study was impressive and understated. Diabetes management should be a special category in any revised ezetimibe prescribing guidelines, noting a large percentage of patients in the high risk category have diabetes.

### **Term of Reference 3**

Stakeholders expressed views on cost-effectiveness and the appropriate comparator in a cost-effective analysis of ezetimibe, including:

- Up-titration of statin monotherapy is not a valid comparator as ezetimibe should be used second-line. Ezetimibe has a special treatment role for high risk patients.
- The most appropriate non statin comparator is cholestyramine.
- The only other therapy to allow patients to achieve LDL targets in difficult clinical scenarios (e.g. statin intolerance and genetic dyslipidaemia) is PCSK9 inhibition which is expensive and only available for homozygous familial hypercholesterolaemia. PCSK9 inhibitors would be appropriate comparators in a cost-effectiveness analysis.
- Report conclusions on cost-effectiveness rely on assumptions and analysis that would be difficult to sustain in a new listing submission.
- Suggested alterations to the time horizon of the model and comparator in the original submission are at variance to PBAC guidelines (Version 5).

### ***Post-market review process***

- Support for the Post-market Review (PMR) Framework and acknowledgment that the Review has followed the procedural guidelines in the Framework, resulting in greater consultation and predictability.
- The Review should give equal consideration to patient health outcomes as to treatment safety and efficacy.
- Stakeholders acknowledged PMR goals including improving the quality use of medicines, PBS viability and patient safety. Clinicians should be prescribing robustly evidence based medicines in pursuit of improved patient treatment outcomes.
- Implementation of outcomes from PMRs should be collaborative over appropriate timeframes. The process of implementing review outcomes is not resolved through the PMR Framework.
- Communication and consultation associated with implementation of PBAC outcomes from PMRs needs improvement to minimise disruption to stakeholders
- There was insufficient time to review the new data introduced in the final Report.

### ***Pricing policy***

- The formulary separation of drugs (F1 & F2) for clinical and cost-effectiveness may be eroded by the Review. Erosion of pricing policy would have ramifications.
- Referencing the price of ezetimibe (F1 medicine) against statins (F2 medicine) was raised. Ezetimibe will soon be off patent and it would be appropriate for price reductions to occur via agreed measures applied to F2 medicines rather than other means.
- Questioned the time and expense involved in review of a medicine approaching patent expiry and associated price reductions.

### ***Quality of evidence***

- The same evidentiary standards that apply to PBAC evaluations should apply to PMRs.
- The Review makes recommendations using data and analysis which do not represent the full body of evidence and the data may not be as robust as that required in a new listing submission. There is a need for greater data collection and sharing.
- An appropriate evidence base is needed when making value for money recommendations, including evidence on the applicability to the Australian population, patient outcomes and utilisation.