

Medicines Australia's submission on the Draft Report of the Ezetimibe Post Market Review

Medicines Australia (MA) welcomes the opportunity to make a submission to the Draft Report of the Post-Market Review of Ezetimibe, a medicine listed on the PBS for the treatment of high cholesterol associated with cardiovascular disease.

MA is the peak organisation representing the research-based pharmaceutical industry in Australia. Our members comprise over 80% of the prescription medicines market by value and play an integral role in delivering better health outcomes for Australians. Medicines Australia's members include sponsors who manufacture and supply medicines affected directly and indirectly by the ezetimibe review.

This is the first full review and report following the recently agreed post-market reviews framework and therefore MA is considering the process alongside the review itself. MA will highlight considerations for the potential consequences of a post market review to patients, clinicians and the industry and also the impact of the review on well-established pricing mechanisms, which may fundamentally alter the integrity of the two formulary system that underpins the PBS.

MA believes that ezetimibe review has been well served by the process outlined in the post-market reviews framework. Stakeholders received valuable opportunities to contribute to the review, including a stakeholder forum. The breadth of this consultation is evident in the approach taken in the report's discussion of how to improve the treatment of high cholesterol in the context of delivering optimal health outcomes. MA members affected by this review support the following advice (I and II) provided in the report and would be supportive of any initiatives that arise to address them:

- I. Education is needed to improve the quality use of lipid lowering medicines
- II. PBS restrictions on lipid lowering medicines should be eased based on the available evidence

In relation to this review, and post market reviews more broadly, MA would also like to raise the following issues (III, IV and V) for PBAC consideration:

- III. Evidentiary requirements for post market reviews
- IV. Consequences on PBS policy and the architecture of PBS reforms
- V. Procedural considerations for the implementation of outcomes following PBAC recommendations

I. Education is needed to improve the quality use of lipid lowering medicines

MA members involved in the research and development of medicines to treat cardiovascular disease (CVD) note that it remains a leading cause of mortality and morbidity in Australia. Important advances in hyperlipidaemia treatment in recent years, could further reduce the significant burden that heart disease imposes on public health.

MA acknowledges the complexity of inferring compliance concerns based on the data provided. However MA strongly supports the importance of quality use of medicines and would be supportive of any measures aimed at improving patient adherence to medicines that in turn

improves broader health outcomes. The development of NPS MedicineWise or similar programs for prescribers and patients on the importance of adherence to PBS restrictions and the need for continuous treatment to lower LDL would be welcome.

MA would be pleased to work with other stakeholders in developing such a program, which could also serve as a useful model for other chronic diseases where adherence and compliance could also be improved.

II. PBS restrictions on lipid lowering medicines should be eased

Affected MA members note the reference group's conclusion that lipid lowering therapy is a mature market and a well-established area of clinical practice. For this reason, we would support removal of the General Statement on Lipid Lowering Drugs from the PBS and the easing of restrictions on lipid lower therapies on the basis of the clinical and real world experience considered in this review.

III. Evidentiary requirements of post market reviews

MA reaffirms our position that reviews must be assessed using the same evidentiary standards that apply to all PBAC evaluations. It is essential that Australia continues to assess both existing and future treatments with clear, consistent standards, to ensure that Australian patients have the best opportunity to access the medicines that they need

MA has expressed concerns that previous reviews have made recommendations based on data and analysis that do not represent the body of evidence and therefore would not have met the evidentiary standards that that PBAC would normally expect from submissions for the PBS listing of new products. It is critical that the appropriate evidence base is used in the making of recommendations on value for money and this should include consideration of the generalisability and applicability to the target population, that is, the Australian population.

Nevertheless, based on the analysis from the ezetimibe review, the draft report confirms that the use of ezetimibe on the PBS is largely consistent with both PBS restrictions and clinical guidelines, i.e. as a second line agent that should be used following the maximally tolerated dose of a statin. MA member companies directly and indirectly impacted by the review agree with this conclusion.

IV. Consequences on PBS policy and the architecture of PBS reform

However, MA is concerned that the analysis undertaken as part of the review results in contestable advice on the choice of comparator and the methods of extrapolation. Specifically that this has potential unintended impact and possible negative effect on PBS policy. For example, where the report advises that ezetimibe should compare to doses of high potency statin monotherapy. This highlights the ongoing issue raised by MA on the methods for appropriate selection of comparators for the purpose of PBAC decision making; as discussed during the recent revision and finalisation of PBAC guidelines version 5. The guidelines currently state that comparators should be selected based on: "*the therapies most likely to be replaced in clinical practice*" or, in the context of a review, the therapies likely to be used if a product were withdrawn from the PBS (Section 1.1.3 pg. 13).

The report also appears to apply a different approach to that recommended in the Guidelines for translating and extrapolating the findings of clinical trials that do not fit the relevant PBS population. The sponsor of ezetimibe consider the approach to be at odds with accepted methods for extrapolation and will respond directly to this in their submission. For example; the draft report makes recommendations to alter the time horizon for modelling ezetimibe's cost effectiveness when section 3A.2 pg. 67, of the guidelines recommends: *Where there is evidence that a treatment affects mortality or long-term/ongoing quality of life, then a lifetime time horizon is appropriate.*

Further, these issues risk the potential unintended consequence of eroding the separation of the F1 and F2 formularies for clinical and cost effectiveness comparisons. This inadvertently undermines the intent of PBS reform that created the F1 formulary for single brand medicines undergoing value-based assessment of cost effectiveness; deliberately de-linked from the F2 formulary, created to harness competition and drive savings in the multi-brand, post-patent market. Additionally, re-linking the formularies for clinical and cost comparisons creates unintended evidence and regulatory barriers for new entrants to the Australian market.

V. Procedural considerations for the implementation of outcomes of a review following PBAC recommendations

Finally, MA reiterates that any outcomes that might arise from this review must be implemented in a collaborative manner over an appropriate timeframe, to minimise the risk of disruption to stakeholders. MA has raised previously through the Access to Medicines Working Group (AMWG), and in other fora, that the procedure for the implementation of PBAC outcomes is deficient and requires improvement. Recommendations that have a material impact on a sponsor or other stakeholders should enable adequate time for the full range of rights and responses to be explored.

The Industry and Government jointly developed the Post Market Review framework through the AMWG, to provide a reliable structure against which to conduct reviews. The ezetimibe review demonstrates that the framework is a useful guide on how to manage the process. However, the AMWG noted that further work was required to resolve the process for the implementation of outcomes from a review to ensure a fair and effective process. MA reaffirms our interest in progressing this matter.

Conclusion

Medicines Australia acknowledges that the post market review framework provides a valuable guide on the process to conduct post market reviews.

With regard to the specific issues relating to ezetimibe, the draft review report finds that ezetimibe is generally used within restriction and that this use is well aligned to clinical guidelines. Further, the report acknowledges that the IMPROVE-IT trial validates the relationship between LDL-C reduction and cardiovascular event reduction with ezetimibe that had underpinned the PBAC's past positive recommendations on ezetimibe's cost.

Nevertheless, the findings from the review of ezetimibe raise some specific concerns relating to: evidentiary requirements for demonstrating, and questioning, cost-effectiveness from the data analysis, potential unintended impacts on PBS policy and the architecture of PBS reform, and

concerns regarding the procedural deficiencies for the implementation of outcomes of PBAC recommendations.

Medicines Australia Thanks the Post Market review team for its rigor in adherence to the review framework and is keen to work with the Government to address the ongoing issues highlighted above in forthcoming reviews and future policy work through the AMWG.