Appendix F – Ezetimibe Stakeholder Forum Outcome Statement

DEPARTMENT OF HEALTH

REVIEW OF EZETIMIBE STAKEHOLDER FORUM

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Background and Purpose

During 2016, the Australian Government is conducting a Post-market Review of Ezetimibe, which is listed on the Pharmaceutical Benefits Scheme (PBS) for the treatment of high cholesterol in certain patient populations. The Review is focused on the cost-effectiveness of ezetimibe in the context of the latest available evidence and best clinical practice. As part of the Review process, the Reference Group of the Post-market Review of Ezetimibe convened a targeted stakeholder consultation forum in Canberra to present initial findings of the Review's evidence evaluations and elicit stakeholder feedback on these findings.

The forum program included presentation of findings by the Reference Group Chair, Emeritus Professor Lloyd Sansom, followed by discussion, and was structured around the Review's three Terms of Reference and questions identified by the Reference Group.

Forum participants included representatives from medicine sponsors, Medicines Australia, the Pharmacy Guild of Australia, NPS MedicineWise and Diabetes Australia.

Douglas Smith from Tempo Strategies facilitated the forum, which was scribed by Emma Pankhurst. Douglas and Emma prepared this summary report.

Term of Reference One - Utilisation

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.

Presentation on Utilisation Evidence

Professor Sansom outlined the current PBS restrictions for ezetimibe, which are based on an absolute risk approach. The evidence evaluation of utilisation focused on the period 1 April 2014 to 1 April 2015, during which time 45,645 patients were initiated on ezetimibe monotherapy or combination use with a statin. The evaluation identified two cohorts:

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

Other findings from the review of the utilisation data included:

- for Cohort 2, a significant proportion (70%) had not changed statin dose in the two years preceding ezetimibe initiation
- Cohort 1 (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 and may indicate either:

    - significant use outside PBS restrictions; or
    - a prior history of statin or other LLT use beyond the two years prior to the study period
- for both cohorts, there were low levels of persistence for all LLTs after initiation on ezetimibe, with 44% of Cohort 1 and 12% of Cohort 2 ceasing all LLTs in the 12 months following initiation of ezetimibe.

In discussing the methodology for the analysis of the utilisation data and the true size of the statin contraindicated population, representatives for the sponsor suggested the use of a different denominator for the study, and agreed to provide further information on this to the Review Secretariat.

In relation to the study findings that 70% of Cohort 2 patients had not had their statin dose increased, it was suggested that this is similar to the experience globally, and that clinicians are choosing to not titrate to the maximum tolerated dose, which may be sub-optimal in terms of low-density lipoprotein cholesterol (LDL-C) reduction outcomes. This may be to avoid side-effects such as muscle aches and pains.

While contraindication to statins remains a valid reason for initiating ezetimibe without first trialling a statin, the negative publicity from the *Catalyst* program (ABC, October 2013) has had a significant impact on patient perceptions and preferences (although it predates the data period used in this study).

Reference Group Questions

The Reference Group identified questions for discussion at the forum.

Question 1

What might be the rationale for initiating a Fixed Dose Combination (FDC) of ezetimibe with a statin, without first trialling a statin alone?

Participants suggested that the figure of 15% (of patients initiated without a history of statins or other LLTs) needs to be understood in the context of:

- the number of patients who are genuinely contraindicated
- the number of patients who had a history of statins or other LLTs beyond the two years preceding initiation of ezetimibe
- the number of patients who were dispensed statins privately as the price for some products is below the general co-payment
- the number of patients who are prescribed ezetimibe and whose scripts are not dispensed – this was considered to be a very small percentage and not highly relevant.

Some clinicians commented that initiation to a statin + ezetimibe combination without a statin trial may occur in the clinical situation where LDL-C is high and needs to be reduced quickly.

Question 2

What evidence is available to assist in determining the size of the population truly contraindicated to statins?

While participants were not able to point to specific sources in discussion, it was acknowledged that there were studies available and participants agreed to provide suggestions to the Review Secretariat.

It was suggested that intolerance is somewhat different from contraindication. Experience indicates that while a large number of patients suggest that they are intolerant, only a small proportion are, and information from trials shows that 1-5% are intolerant. It is also possible that up to 10% are partially intolerant.

Term of Reference Two - Guidelines

Review recent clinical guidelines for the treatment of hypercholesterolaemia and compare this to how ezetimibe is currently used on the PBS.

Presentation on Clinical Guidelines

Professor Sansom outlined the findings from the review of clinical guidelines. The main conclusions from this review were:

- all guidelines continue to recommend statins as first line therapy reserving non-statins including ezetimibe for second line therapy except in those patients intolerant / contraindicated to statins
- this recommendation results from the very large data on the clinical benefits of statin use compared to the limited data on patient-relevant outcomes for ezetimibe.

Reference Group Questions

Question 1

The Silverman et al. systematic review and meta-analysis suggests the order of lipid lowering therapy used to achieve a reduction in LDL-C is not important in reducing patients' risk of cardiovascular events. Why then should ezetimibe continue to be positioned as second line therapy through PBS restrictions?

Comments made by participants in relation to this question included:

- its use is supported by internationally-accepted standards and guidelines
- while the Silverman et al. paper showed that lowering LDL-C resulted in a greater reduction of risk, it did not discuss the ordering of these drugs
- recent EU and USA guidelines promoting the current hierarchy in treatment have also been supported by other papers
- 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 PBS listing.

Question 2

Is the General Statement for Lipid-Lowering Drugs still relevant and if so should it be revised?

In discussing this question, participants noted that while the General Statement did not explicitly refer to ezetimibe, it did cross-reference the ezetimibe PBS restrictions, and as had been previously discussed in the forum, the PBS restrictions do not fully reflect prescribing practice.

While it was suggested that the General Statement remains relevant, it was also noted that PBS restrictions can enable clinical guidelines only as far as considerations of cost-effectiveness allow (cost-effectiveness is a legislative requirement of the *National Health Act 1953*).

Participants also emphasised the importance of lifestyle changes such as healthy diet and exercise in conjunction with LLT.

Other comments included the need for clinician education on the guidelines as well as a focus on patient compliance.

Some participants commented that the General Statement is complicated and revision may be beneficial.

Term of Reference Three – Clinical Studies

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.

Presentation on Clinical Studies

Professor Sansom outlined the findings from the review of a number of key clinical studies, which demonstrate that outcomes are either inconclusive or not generalisable to the Australian population. The Reference Group's main conclusions from this review were:

- The clinical outcomes of the IMPROVE-IT trial confirm the acceptability of absolute reduction in LDL-C as a valid surrogate for the reduction of the relative risk of major vascular events. The reduction in event rate was as predicted by the known relationship between absolute reduction in LDL-C and the relative risk reduction.
- 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.

Reference Group Questions

Question 1

The Review aims to comprehensively consider the most recent relevant evidence. Is there further recent evidence that should be considered by the Reference Group prior to making findings?

Participants agreed to provide suggestions of other relevant studies to the Review Secretariat. Specific comments made by participants included:

- in using any studies, it is important to consider the depth of evidence and applicability to the Australian context
- despite its limitations, IMPROVE-IT is the most up-to-date and well-run study, and also addressed questions in relation to the safety of ezetimibe
- the experiences of failed studies (studies that did not demonstrate outcomes) are also relevant to this Review.