MEDICINES Australia

Better Health through Research and Innovation

Submission to the Consultation on the Draft Terms of Reference for the *Post-Market Review Ezetimibe*

13 November 2015

Introduction

Medicines Australia welcomes the opportunity to comment on the Draft Terms of Reference of the Post-Market Review of Ezetimibe. Medicines Australia represents the research-based pharmaceutical industry in Australia, which brings new medicines, vaccines and health services to the Australian market. Our members are responsible for the discovery, research, development and commercialisation of up to 86% of medicines currently available on the Pharmaceutical Benefits Scheme (PBS) by value. Medicines Australia's members include sponsors who discover, develop, manufacture and supply the medicines affected directly and indirectly by the proposed ezetimibe review.

This review and the concurrently announced review of Chronic Obstructive Pulmonary Disease (COPD) Medicines are the first initiated under the recently agreed framework for the post-market review programme. This framework was developed between Medicines Australia and the Department of Health through the Access to Medicines Working Group (AMWG). This framework introduced very welcome rigour and certainty into the review process. Additionally, it was agreed by the AMWG that further guidance and clarity could be provided on:

- the evidentiary requirements for reviews, or
- the implementation of review outcomes.

These two reviews represent an important opportunity to build confidence in the framework, to ensure that it is applied consistently and to ensure further progress on the above mentioned outstanding issues can be made through these reviews and the AMWG, to the benefit and satisfaction of all parties.

Medicines Australia acknowledges the government's goals in conducting reviews, namely the desire to improve; patient safety, PBS viability, the understanding of utilisation & cost-effectiveness and quality use of medicines (QUM). Medicines Australia shares the belief that reviews should help to achieve the aims of the National Medicines Policy which also include timely access to medicines at a cost individuals and the community can afford and maintaining a responsible and viable pharmaceutical industry.

This response considers these objectives while reviewing the draft terms of reference proposed for the review. In addition to the overarching recommendation that the review adhere to the post-market review framework, the specific recommendations of this response relate to:

1. Broadening the purpose of the review to consider safety, efficacy, health outcomes and QUM
2. Broaden the scope of term of reference 1 to ensure that utilisation and other data is fit for purpose and available to all stakeholders
3. Broadening the evidence considered, beyond just outcomes studies, to ensure improved outcomes for patients
4. Stakeholders are provided sufficient time to; consider the terms of reference, the literature and data available to them, consult adequately with constituencies and develop responses.
5. Convene a stakeholder forum prior to the close of submissions to enable two way dialogue on.
6. Ensure that the implementation of the review considers all appropriate options that assess the benefit of ezetimibe to Australians with cardiovascular disease and are considered in the context of the post-market review programme goals.
7. Process considerations, in particular the process for the implementation of outcomes, should continue to be addressed through the AMWG

A. Patients with high cholesterol require treatment options to reduce the risk of serious events

Cardiovascular disease (CVD) imposes a substantial burden on Australians. It affects more than three and a half million Australians[1] and accounts for nearly 50,000 deaths[2]. High cholesterol causes a third of the CVD's disease burden[3]. Despite the treatment of over 2 million patients with statin therapy on the PBS[4], less than half of patients with high cholesterol take medication for their condition[5] and only half of these reach their recommended cholesterol target levels[6].

Ezetimibe inhibits the absorption of cholesterol in the gut and its mechanism of action is different to that of statins and other cholesterol reducing compounds[7]. It is listed on the PBS for 11 different restrictions as follows:

Co-administration with a statin in patients inadequately controlled on a statin and
• who have
  ○ heart disease
  ○ diabetes mellitus
  ○ peripheral vascular disease
  ○ heterozygous familial hypercholesterolaemia
  ○ systematic cerebrovascular disease
  ○ family history of coronary heart disease
  ○ hypertension
• are contraindicated to a statin
• developed clinically important adverse event during stating treatment
	Homozygous sitosterolaemia	Homozygous familial hypercholesterolaemia in combination with a statin

It is also listed in combination with statins, with restrictions similar to those above. The PBS schedule includes clear definitions of "*inadequate control*" at the maximum tolerated dose of a statin and "*clinically important adverse events*" to guide appropriate prescribing.

The restrictions contain the use of ezetimibe to situations where the consideration of a statin or a higher statin dose is not an option because the patient is at the maximum tolerated dose of statin, is contraindicated to statin or has a condition where statins are not appropriate.

One in ten Australians have a precaution against the prescribing of a statin[8] so there is a recognised clinical need for treatment options beyond 1st-line statin therapy. Ezetimibe has been able to address at least part of this important clinical need. Approximately 300,000 Australians currently take ezetimibe alone or in combination with statins.

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[1] Australian Bureau of Statistics. Australian Health Survey 2011/2012

[2] Australian Bureau of Statistics. Causes of Death 2011 (3303.0). March 2013

3 Begg S, Vos T, Barker B, Stevenson C, Stanley L, Lopez AD, 2007. The burden of disease and injury in Australia 2003 PHE 82 Canberra: AIHW.

[4] http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2012-07/review-of-statin-therapies.pdf

[5] Heart Foundation. Heartwatchsurvey 2011.

[6] Australian Bureau of Statistics, 43640DO010_20112012 – Australian Health Survey: Biomedical Results for Chronic Diseases, 2011–2012 (Released 5 Aug 2013; accessed: 11 Feb 2015). Calculated: Prevalence of dyslipidaemia, Persons (estimate): Using lipid medication and has abnormal lipid levels 976,700 (52.2%) Using lipid medication and has normal lipid levels 894,800 (47.8%) TOTAL using lipid medication 1,871,500.

[7] EZETROL (ezetimibe). Australian Approved Product Information. Sydney: MSD. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-05310-3&d=2015103016114622412

[8] In 2011–12, around 1.9 million (11.0%) people aged 18 years and over had abnormal or elevated levels of ALT in their blood, Australian Bureau of Statistics, 43640DO007_20112012 – Australian Health Survey: Biomedical Results for Chronic Diseases, 2011–2012 (Released 5 Aug 2013; accessed: 11 Feb 2015)

B. The terms of reference and supporting information should provide more context to stakeholders as to why this review was initiated

The framework for post market reviews states that reviews can be initiated at any time and triggered by a number of issues identified through a number of sources (the PBAC, DUSC, the Minister of Health, the Senate or stakeholders).

The framework explains the purpose of reviews as follows:

> The post-market review process provides a mechanism for medicines to be considered in the full and current treatment context. This includes actual utilisation, comparative efficacy, treatment guidelines, health outcomes, and for measures to be implemented that address concerns that may have arisen, for example, improving education around medicines and their use, or revised restrictions.

As described, the post market review programme was established to achieve five main goals. As such, the triggers and the goals of each review may be different. This is demonstrated in a comparison of three recent reviews at Appendix 1.

The COPD review is primarily focussed on QUM issues, and the diabetes review focussed on changes in clinical management. Medicines Australia has consistently asserted that Reviews should be held to the same standards of evidence and objectivity required of standard PBAC reviews. As such, any consideration of expenditure should be made in the context of whether the expenditure is cost-effective, rather than expenditure being a concern in and of itself.

It is also worth noting that although long-term outcomes data was not available when the review was first identified (in November 2013), this is no longer the case. The landmark IMPROVE-IT study of ezetimibe in 18,000 ACS patients was recently concluded. This is one of the largest outcomes trials ever completed in cardiovascular disease. It established that LDL-C reduction has significant benefit in reducing cardio-vascular events, even where such reduction is achieved through the use of ezetimibe rather than statins[9].

The purpose of the ezetimibe review provided in the terms of reference appears to be focused exclusively on cost-effectiveness. The ezetimibe terms of reference simply state that the purpose is to "review the cost-effectiveness of ezetimibe, in the context of the latest available evidence and best clinical practice".

In contrast, the purpose statements of other reviews refer to safety, efficacy, quality use of medicines and health outcomes. This exclusive focus on cost-effectiveness is concerning given the trigger that "PBS expenditure on the drug was high".

Like other reviews where treatment targets where included in the review consideration (e.g. HbA1c in the diabetes review), there is now sufficient evidence for LDL-C reduction to be considered as an objective for a review such as this in pursuing better treatment outcomes.

It is premature to put forward comparators before the scope of the review has been finalised

While other reviews list the classes and products that the review will consider, the ezetimibe review also lists "medicines considered as comparators". This is appears to be premature given that the population or restriction within which the review will focus has yet to be established, hence it is difficult to know how the terms of reference can already dictate which comparator might be appropriate. Medicines Australia recommends re-consideration of other possible relevant comparators in the context of the finalised scope of the review.

[9] Cannon et al (2015) Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med 18;372(25):2387-97.

Recommendation 1

Medicines Australia recommends broadening the purpose of the review to consider safety, efficacy, health outcomes and QUM. Specifically:

From: The purpose is to review the cost-effectiveness of ezetimibe, in the context of the latest available evidence and best clinical practice.

To: The purpose is to review the utilisation, safety, efficacy and cost-effectiveness of ezetimibe to ensure the most appropriate management of hypercholestrolaemia in clinical practice through the reduction of LDL-C and to achieve optimal health outcomes and support quality use of medicines, in the context of the latest available evidence and best clinical practice.

C. The terms of reference should be broadened

1. *Review existing Drug Utilisation Sub-Committee (DUSC) data and consider additional data sources that would inform on the current utilisation of ezetimibe.*

A DUSC utilisation analysis (October 2014) has been conducted comparing the predicted versus actual use of the low dose ezetimibe with simvastatin FDC (Vytorin 10/10 and 10/20mg) following the change in restriction from use after 40mg of simvastatin to use after maximum tolerated dose.

The outcomes of this review were inconclusive, with DUSC unable to identify any inflection in the use of these presentations after this change.

It should also be noted that these low dose presentations represent a small proportion of overall ezetimibe use. The majority of ezetimibe use is with higher dose statins where there is likely little scope for further statin up titration. DUSC acknowledged that it is difficult to assess when a patient has been treated with the maximally tolerated dose of a statin.

This DUSC review in isolation does not appear to be a conclusive trigger for a review, given its narrow scope and inconclusive findings. It would be useful for stakeholders to understand if there are further data or other unstated concerns on which the PBAC based its recommendation to initiate this review.

The co-packs and combinations that the PBAC identified as potential drivers of out of restriction ezetimibe use, were listed in December 2013 (ATOZET co-pack containing atorvastatin and ezetimibe), January 2015 (ROSUZET co-pack containing rosuvastatin and ezetimibe) and August 2015, (ATOZET fixed-dose combination of atorvastatin and ezetimibe). If utilisation of these products is to inform the review it may be more useful to have the standard two years of data available for DUSC analysis, to provide more valuable utilisation evidence.

Recommendation 2:

Broaden the scope of terms of reference 1 to ensure that utilisation and other data is fit for purpose and available to all stakeholders

From: Review existing Drug Utilisation Sub-Committee (DUSC) data and consider additional data sources that would inform on the current utilisation of ezetimibe.

To: Consider data sources that are aligned to the purpose and scope of the review. Ensure that any utilisation of ezetimibe is considered in the context of the utilisation of other statin therapies. Identify data sources to inform whether patients are currently being treated in line with the current ezetimibe restrictions.

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

Recommendations regarding the use of ezetimibe made in the peak Australian guidelines for the treatment of hypercholesterolaemia are summarised in Appendix 2. The current PBS restrictions, which position ezetimibe as a second-line treatment following statins for patients at high or very high cardiovascular risk, are consistent with what these guidelines recommend.

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.*

Similar to TOR 1, this term of reference is narrow, confining the review to a single study of cost-effectiveness. The meaning and implications of the results of this study, would be better understood in the context of a broader review of the literature.

Recommendation 3

Broadening the evidence considered beyond just outcomes studies, to ensure proper context**.** Reword term of reference 3 as follows:

From: 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

To: Collate and evaluate all clinical studies of ezetimibe, other cholesterol lowering medicines and any other relevant publications, and use this data to review the cost-effectiveness of ezetimibe in relevant populations.

D. The review process should allow for adequate consultation and appropriate outcomes

As outlined above, this review has potential consequences and requires input from a large number of patients, their representative groups, treating clinicians, other health professionals and sponsors. Given the complexity of the review, Medicines Australia suggests that the minimum six week period for stakeholders to respond to the final terms of reference will be the minimum period required, and a longer period for comment should be considered, particularly should this be called for by stakeholders.

Medicines Australis notes that the draft terms of reference were not distributed initially to all relevant stakeholders, prior to the announcement of this consultation. Medicines Australia

commends the Department of Health for providing an additional two weeks for stakeholders to consider these terms and additional information on the scope and triggers for the review.

To ensure full participation through the submission process, MA requests that the Department reach out to all relevant stakeholders when announcing the final terms of reference and call for submissions. A list of organisations are provided to assist. (Appendix 3).

Recommendation 4

Medicines Australia requests that sufficient time is provided to give stakeholders the opportunity to consider the terms of reference, consider the literature and data available to them, consult adequately with constituencies and develop their responses.

Given the complexity of the review, the clinical importance of this therapy and the vast range of stakeholders impacted, Medicines Australia recommends holding a stakeholder forum during the review to ensure all views are appropriately considered. This is in line with the framework provision in the case of "significant public interest, complex reviews, or large scale reviews".

Recommendation 5

A stakeholder forum should be convened for this review before the deadline for stakeholder submissions.

Finally, the outcomes of this review may lead to a range of recommendations. Medicines Australia suggests that these consider all types of responses, including QUM related improvements in the information circulated to prescribers and patients on CVD management together with other changes that might be considered. Medicines Australia also believes that recommendations should be considered in the context of how they deliver on the goals of the post-market review programme, namely

- *Improved patient safety through better understanding of adverse events and medicine-related harms.*
- *Ensuring the ongoing viability of the PBS through targeted medicines usage and avoiding preventable wastage or inappropriate prescribing.*
- *A better understanding of medicines utilisation, to review intended clinical benefit and inform medicines evaluation processes.*
- *Ongoing cost-effectiveness, including through better management of clinical and economic uncertainty.*
- *Overall improvements to the quality use of medicines and education for patients and prescribers.*

Medicines Australia also recommends further dialogue on agreeing the process for the implementation of outcomes through the AMWG.

Recommendation 6

Ensure that the implementation of the review considers all appropriate options that assess the benefit of ezetimibe to Australians with cardiovascular disease and are considered in the context of the post-market review programme goals.

Recommendation 7
Process considerations, in particular the process for the implementation of outcomes, should continue to be addressed through the AMWG

Appendix 1

(initiated)	***Ezetimibe review*** (Oct 2015)	***COPD review*** (Oct 2015)	***Diabetes review*** (Aug 2012)
Trigger	In November 2013, the PBAC expressed concern that the listing of ezetimibe with statin co-packs and combination products on the PBS may direct use away from optimal dose titration of statins. The PBAC also noted that in contrast to statins, there are no long term patient relevant outcome data for ezetimibe, and that PBS expenditure on the drug was high.	In October 2013, the Drug Utilisation Sub-Committee of the Pharmaceutical Benefits Advisory Committee (PBAC) reviewed the Pharmaceutical Benefits Scheme (PBS) utilisation of indacaterol and budesonide/efomoterol for COPD. The review identified co-administration of multiple long-acting beta agonist (LABA) products in some patients, which was considered a significant quality use of medicines issue. In August 2015, the PBAC recommended a Post-market Review of COPD Medicines, noting that a number of new combinations, including long-acting muscarinic antagonist (LAMA)/LABA and LABA/inhaled corticosteroid (ICS) combinations, have been listed recently on the PBS and that there was concern about use of multiple products.	In 2012, the Drug Utilisation Sub-committee (DUSC) requested a complete review of diabetes medicines. The Pharmaceutical Benefits Advisory Committee (PBAC) agreed to the Review due to the considerable recent changes in diabetes management, including the PBS listing of a number of new anti-diabetic medicines
Purpose	Review the cost-effectiveness of ezetimibe, in the context of the latest available evidence and best clinical practice.	Review the utilisation, safety, efficacy and cost-effectiveness of PBS listed COPD medicines, and to address quality use of medicines concerns associated with the apparent use of multiple products.	Systematically evaluate the body of clinical evidence regarding diabetes interventions to ensure the most appropriate management of diabetes in clinical practice. Ensure that patients are using the most appropriate medicines and products, effectively, and safely, to achieve optimal health outcomes and support quality use of medicines.
Scope	Medicines to be included in this Review are ezetimibe and ezetimibe co-pack/combination products listed or considered for listing on the PBS. Medicines considered as comparators may include other lipid lowering medicines, such as statins and bile acid sequesterants.	Medicines listed on the PBS for the treatment of COPD only: Aclidinium, Glycopyrronium, Indacaterol, Indacaterol + Glycopyrronium, Tiotropium, Umeclidinium, Umeclidinium + Vilanterol. Medicines listed on the PBS for the treatment of COPD and asthma: Beclomethasone, Budesonide, Budesonide + Eformoterol, Ciclesonide, Fluticasone, Fluticasone + Salmeterol, Fluticasone + Vilanterol, Ipratropium, Prednisone, Salbutamol, Terbutaline, Theophylline.	Medicines used in the management of type 2 diabetes [it was later clarified that the scope of the review only extended to oral medications]

Appendix 2

The peak Australian guidelines for the treatment of hypercholesterolaemia and the recommendations therein related to the use of ezetimibe are:

Primary prevention: The National Vascular Disease Prevention Alliance (NVDPA) Guidelines for the Management of Absolute Cardiovascular Disease Risk which were published in 2012 (https://strokefoundation.com.au/what-we-do/treatment-programs/clinical-guidelines/guidelines-for-the-assessment-and-management-of-absolute-cvd-risk).
The NVDPA primary prevention guidelines categorise patients into high, moderate and low risk on the basis of an assessment of absolute CV risk generated from the Framingham risk equations. The recommended LCL-C target is < 2 mmol/L across the board. Drug therapy is recommended as routine for all high risk patients and second-line to diet and lifestyle modification in select moderate risk patients. Whilst an absolute risk assessment approach in not adopted to determine eligibility to PBS-subsidised drug treatment, all patients eligible for ezetimibe on the PBS would fall into a risk category where drug therapy is recommended in the NVDPA guidelines. The NVDPA guidelines recommend statins as first-line drug therapy. If LDL-C levels are not sufficiently reduced on maximal tolerated doses of statin, it is recommended that one or more of ezetimibe, bile binding resion or nicotinic acid may be added. For those intolerant to statins, it is recommended that one or more of ezetimibe, bile binding resion or nicotinic acid may be used.
Secondary prevention: The Heart Foundation and Cardiac Society of Australia and New Zealand (CSANZ) Reducing risk in heart disease: An expert guide to clinical practice for secondary prevention of coronary heart disease published in 2012 (http://www.heartfoundation.org.au/SiteCollectionDocuments/Reducing-risk-in-heart-disease.pdf).
The secondary prevention guidelines recommend statin therapy for the management of lipids in all patients with CHD (apart from in exceptional circumstances). The recommended goal is LDL-C < 1.8 mmol/L. The guidelines note that patients taking statins may experience common (muscle aches and pains) and rare (rhabdomyolysis) side effects. Ezetimibe is noted to reduce the concentration of LDL-C by 15-20% as monotherapy or when added to a statin. Longer safety data is considered satisfactory.

Familial hypercholesterolaemia: The 2013 CSANZ guidelines Guidelines for the Diagnosis and Management of Familial Hypercholesterolaemia (http://www.csanz.edu.au/wp-content/uploads/2013/12/Familial_Hypercholesterolemia_2013.pdf) reference a 2011 publication by Watts et al: “Familial hypercholesterolaemia: A model of care for Australasia” (Watts et al. Atherosclerosis Supplements 12 (2011) 221–263).
The FH model of care includes LDL-C targets for adults, adolescents and children with FH based on level of risk. It is recommended that achieving these targets will require pharmacological therapy with a statin with or without ezetimibe. It is recommended that statins be used as first-line therapy and should be up-titrated to the maximally recommended tolerable dose that achieves the recommended therapeutic target. This guidelines notes that higher risk patients who require greater lowering of LDL-C will require other drugs, especially ezetimibe, but also niacin, fenofibrate and bile acid binding resins.

Appendix 3

Organisation

Heart Foundation
Stroke Foundation
Stroke Foundation
Diabetes Australia
Diabetes NSW
Consumers Health Forum
Kidney Health Australia
Pharmacuetical Society of Australia
Pharmacy Guild
AMA
RACGP
Rural Doctors Association Australia
Baker IDI