MSD response to the Draft Review Terms of Reference: Ezetimibe

MSD welcomes the opportunity to comment on the Draft Terms of Reference of this review.

MSD believes that this review will show that:

- The use of ezetimibe-containing products on the PBS is consistent with PBS restrictions, clinical guidelines, and quality use of medicines principles
- Long-term outcomes data from the IMPROVE-IT trial confirm that the LDL-C lowering effect with ezetimibe translates to the reduction in CV events anticipated in all previous PBAC submissions and discussions of ezetimibe, and
- Current Commonwealth expenditure on ezetimibe delivers good value for money

Executive Summary

The framework for post-market reviews states that reviews contribute to achieving the aims of the National Medicine Policy namely:

- timely access to medicines that Australians need, at a cost individuals &the community can afford;
- medicines meeting appropriate standards of quality, safety and efficacy,
- quality use of medicines, and
- maintaining a responsible and viable medicines industry.

MSD is concerned that the current draft terms of reference will jeopardise the review's ability to deliver an outcome consistent with these aims.

The PBAC raised the following concerns in recommending this review:

- the listing of multiple ezetimibe combinations which may reduce optimal dose titration of statins
- the lack of patient relevant outcome data
- high expenditure on ezetimibe.

ROSUZET co-pack and ATOZET FDC were PBS listed in January 2015 and August 2015 respectively, and the results of the IMPROVE-IT outcomes trial were released in Nov 2014. If this review is to provide meaningful insights into these concerns, it cannot do this until sufficient time has passed to generate the data needed to address them.

In addition, budgetary issues do not fall within the remit of the review framework, hence 'high' expenditure cannot be cited as a trigger for a review, unless it relates to usage that is not cost effective or is outside intended utilisation.

In order to ensure that this review can contribute to the aims of the National Medicines Policy, MSD recommends the following changes to the terms of reference (changes in italics):

The **Purpose of the Review** should be refined as follows:
To review the *utilisation, safety, efficacy and* cost-effectiveness of ezetimibe *to ensure the most appropriate management of hypercholestrolaemia in clinical practice and to achieve optimal health outcomes and support quality use of medicines*, in the context of the latest available evidence and best clinical practice.

The following statement in the preamble of the terms: "Medicines considered as comparators may include other lipid lowering medicines, such as statins and bile acid sequesterants" should be removed as it will bias the review's approach and results. Consistent with normal PBAC standards, a comparator cannot be determined until the specific population and utilisation that the review will specifically address has been determined.

The terms of reference must also align the purpose of the review with the data available. If the review is to address recently listed combinations, then sufficient data must be collected to review utilisation (the standard DUSC process is to collect two years of data for this purpose). At the very least, utilisation data up to December 2015 should be considered.

The **Terms of Reference** are changed as follows:

ToR 1: *Analyse the current utilisation of PBS listed ezetimibe-containing presentations using data up to and including December 2015. Analyse this data with respect to subpopulations within the scope of this review. Assess the use of ezetimibe in the context of utilisation of other lipid-lowering therapies. Identify additional sources of evidence to inform whether patients are currently being treated in line with criteria for reimbursements.*

ToR 2: Review recent clinical guidelines for the treatment of hypercholesterolaemia and compare this to how ezetimibe is currently used on the PBS. (no change)

ToR 3: Collate and evaluate *all relevant* clinical studies of ezetimibe *and all relevant publications*, and use this data to review the cost-effectiveness of ezetimibe

The review process must allow for procedural fairness and transparency, therefore MSD proposes additional recommendations to meet the standards for a robust scientific review:

- The affected sponsor should have equal access to any information and analyses assessing utilisation used to inform the review
- Given the complexity of this review, stakeholders and the sponsor should have six months from the release of the finalised terms of reference and the availability of utilisation data to complete their submissions (as opposed to the minimum 6 weeks specified in the review framework)

- Given the complexity of the required cost-effectiveness submission, a pre-submission meeting between DOH, the evaluators and the affected sponsor should be provided to agree on the scope, applicable populations, comparator(s) and modelling assumptions and inputs.

- A stakeholder forum should be convened as part of this post-market review to discuss and align on assumptions regarding current clinical practice in Australia

- Once the Terms of Reference are ratified by the minister, PBAC minutes related to the discussion and finalisation of the Terms of Reference should be made available to stakeholders

Post-market reviews are intended to contribute to the objectives of the National Medicine Policy

This review and that for medicines used to treat chronic obstructive pulmonary disease are the first initiated under the recently-established framework for post-market reviews. This framework states that reviews are intended to contribute to the objectives of the National Medicine Policy[1], namely:

- timely access to the medicines that Australians need, at a cost individuals and the community can afford;
- medicines meeting appropriate standards of quality, safety and efficacy;
- quality use of medicines (i.e. selecting management options wisely; choosing suitable medicines if a medicine is considered necessary; using medicines safely and effectively)[2];
- maintaining a responsible and viable medicines industry.

The framework outlines the type of issues that can trigger a review: clinical efficacy and safety; use that is inconsistent with treatment guidelines and emerging clinical data; use outside of PBS restriction; and cost-effectiveness. The framework also states that post-market reviews provide:

> "…*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*"[3].

The PBAC recommended a post-market review "*to review the cost-effectiveness of ezetimibe, in the context of the latest available evidence and best clinical practice*"[4] as a response to these issues:

1. The listing of ezetimibe with statin co-packs and combination products on the PBS may direct use away from optimal dose titration of statins,
2. In contrast to statins, there are no long term patient relevant outcome data for ezetimibe, and
3. PBS expenditure on the drug was high.

MSD is concerned that the review envisaged by the current draft terms of reference is not consistent with objectives of the NMP:

1. The need for this review is not adequately justified
2. The scope and timing should ensure that a rigorous assessment can be conducted
3. The ToR should be revised to ensure that ezetimibe use can be considered in the full and current treatment context

[1] http://www.health.gov.au/internet/main/publishing.nsf/Content/national-medicines-policy
[2] http://www.health.gov.au/internet/main/publishing.nsf/Content/nmp-quality.htm
[3] http://www.pbs.gov.au/reviews/subsidised-medicines-reviews-files/post-market-review-framework-10-2014.pdf
[4] http://www.pbs.gov.au/info/reviews/post-market-review-ezetimibe

Purpose of the review does not reflect a focus on quality use of medicines

The stated purpose of the post-market review of ezetimibe is "to review the cost-effectiveness of ezetimibe, in the context of the latest available evidence and best clinical practice."[5]

To contribute effectively to delivering the objectives of the NMP, and to be consistent with the post market review framework, the purpose and scope of the ezetimibe review should be specific and include an emphasis on health outcomes and quality use of medicines.

Recommendation 1: the purpose of the ezetimibe review should emphasise health outcomes and quality use of medicines.

From: To review the cost-effectiveness of ezetimibe, in the context of the latest available evidence and best clinical practice

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

The scope and timing of this review should be reassessed to ensure a rigorous assessment can be conducted

The scope of the review pre-supposes conclusions regarding comparators

The post-market review framework noted that "Medicines considered as comparators may include other lipid lowering medicines, such as statins and bile acid sequesterants."

All uses of ezetimibe reflect circumstances where a statin or statin up-titration is not an option; this could be because the patient is at the maximum tolerated dose of statin, has contraindications to statin therapy or has a condition where statins are not appropriate. This is consistent with clinical guidelines which nominate statin as the first line of treatment.

Fundamentally, the selection of a comparator needs to follow a rigorous assessment of what is being replaced in current practice. It is inappropriate to draw any conclusions before this analysis has been made and critiqued through the post-market review process.

[5] http://www.pbs.gov.au/info/reviews/post-market-review-ezetimibe

Recommendation 2: delete the statement "Medicines considered as comparators may include other lipid lowering medicines, such as statins and bile acid sequesterants" as this needs to be assessed and justified as part of the review process.

An analysis of utilisation data should incorporate a minimum 24 month timeframe following listing of the first co-pack presentation

In justifying this review, PBAC expressed concern that listing of ezetimibe with statin co-packs and combination products on the PBS may direct use away from optimal dose titration of statins. These presentations were listed on the PBS 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).

Consistent with standard timeframes for predicted versus actual DUSC analyses, it is important that this review incorporate a review of utilisation data encompassing a minimum 24 months' timeframe following listing of the first of these presentations.

Recommendation 3: initiate the post-market review after an analysis of utilisation of ezetimibe-containing products is conducting that includes PBS data up to and including December 2015.

The ToR should be revised to ensure that ezetimibe can be considered in the full and current treatment context

ToR 1: Utilisation data should not be used in isolation and must be assessed in the context of other lipid lowering therapies

The existing DUSC review was limited in scope (e.g. predicted versus actual for Vytorin 10/10 & 10/20mg related to an extension of listing) – use of this report for the purposes of this review would be insufficient to adequately inform the utilisation of ezetimibe.

Furthermore, the ToR should not be prescriptive on what sources are used to inform utilisation. The source of the data (e.g. existing DUSC data, or additional data sources) is less important; what is more important is the relevance of the data in showing how ezetimibe has been utilised.

It is also important that any analysis of utilisation of ezetimibe should not be viewed in isolation but should be considered in the context of utilisation of other lipid-lowering therapies, in particular those used as second line therapies (e.g. gemfibrozil, fenofibrate, cholestyramine).

An important aspect of this review will be conclusions regarding whether or not patients are trialling maximum tolerated doses of a statin prior to commencing ezetimibe. In this regard, the DUSC report (October 2014) states on pg31: "*The DUSC questioned whether patients are trialling maximum tolerated doses of a statin prior to commencing on the FDC product, as required for the PBS subsidy for hypercholesterolaemia, but noted that utilisation data alone would not be able to quantify this*".

It is important that any assumptions made to derive these conclusions are held to the same level of quality and rigour as Sponsor-led submissions to the PBAC.

Thus additional data sources need to be identified and analysed to inform the evidence-base for any conclusions related to this this ToR. This should also include a consideration of the limitations of statin therapies in clinical practice, for example:

- Patients that have contraindications or precautions to statin therapy
- Patients who might not have reached target lipid levels with maximal doses of statins
- Patients who are intolerant to statins
- Those that develop side effects

Recommendation 4: reword ToR 1 to assess utilisation in the context of other lipid lowering therapies using data up to and including December 2015, and to specify that additional sources of information (other than utilisation data) are needed to inform whether or not PBS restrictions are being adhered to.

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

To: Analyse the current utilisation of PBS listed ezetimibe-containing presentations using data up to and including December 2015. Analyse this data with respect to the subpopulations within scope of this review. Assess use of ezetimibe in the context of utilisation of other lipid-lowering therapies. Identify additional sources of evidence to inform whether patients are currently being treated in line with criteria for reimbursement.

ToR 2: Clinical guidelines and the restricted use of ezetimibe in clinical practice must be reviewed

No changes are recommended to this ToR.

ToR 3: All clinical studies and publications must be used to assess cost-effectiveness of ezetimibe

The current wording of this ToR restricts the cost-effectiveness review of ezetimibe to "recent clinical studies of ezetimibe that report on long term patient relevant outcomes", i.e. IMPROVE-IT study.

It is important to understand that IMPROVE-IT study evaluated the effect of ezetimibe combined with simvastatin in a specific clinical setting:

- High-risk patients presenting with acute coronary syndromes (ACS), i.e. secondary prevention
- Patients whose LDL-C values were within guideline recommendations

The PBS listing for ezetimibe is subject to 11 streamlined authority codes. All of these uses, aside from statin intolerance and severe statin induced adverse events, are in situations where cholesterol levels are inadequately controlled, i.e. not at target.

Therefore IMPROVE-IT study does not provide evidence that is directly applicable for the majority of patients treated with ezetimibe on the PBS. Thus using this study in isolation would be inappropriate.

As discussed previously, the importance of IMPROVE-IT study relates to its conclusions that:

- Addition of ezetimibe to statin treatment further reduces the incidence of CV events
- The magnitude of reduction is directly related to the LDL-C lowering effect, and is consistent with the landmark CTT analysis, which predicts a 23% reduction in the risk of major CV events over 5 years for every reduction of 1 mmol/L in LDL-C

The current wording of this ToR unnecessarily and inappropriately restricts the scope of clinical data that should be considered in reviewing cost-effectiveness. "Long term patient relevant outcomes" whilst being very informative, should not be considered as the sole source of clinically useful data for assessing cost-effectiveness, particularly when the long-term patient relevant outcome data has in fact validated the surrogate measure (reduction in LDL-C) that was used in past submissions.

In order to ensure a robust, scientific analysis required for the evaluation of cost effectiveness, a review of all relevant published literature should be identified and considered in reviewing cost effectiveness. This is consistent with the PBAC guidelines and in line with the intended purpose of this review, namely as suggested by MSD "to review the utilisation, safety, efficacy and cost-effectiveness of ezetimibe and ezetimibe-containing products listed on the PBS, and to consider associated quality use of medicines issues." The entire body of clinical evidence, including data on LDL-C, should be considered, and modelling should be based on the established relationship between LDL-C lowering and reduction in CV events (e.g. using the meta-analysis from the CTT collaboration).

Lastly, the current listing criteria for ezetimibe encompass a total of 11 streamline authority codes, each describing its use in a distinct clinical setting. For clarity, it is critical that the ToR explicitly states which specific patient groups are within the scope of this review.

<u>Recommendation 5</u>: do not restrict what type of data should be used to establish cost effectiveness; explicitly state which specific patient groups are within the scope of this review.

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

To: Collate and evaluate all clinical studies of ezetimibe and all relevant publications, and use this data to review the cost-effectiveness of ezetimibe in the following circumstances:

[ToR to explicitly state which specific patient groups / uses of ezetimibe are within the scope of this review.]

The review process must allow for procedural fairness and transparency

The review process must allow for procedural fairness and transparency, therefore MSD proposes additional recommendations to meet the standards for a robust scientific review:

- The affected sponsor should have equal access to any information and analyses assessing utilisation used to inform the review
- Given the complexity of this review, stakeholders and the sponsor should have six months from the release of the finalised terms of reference and the availability of utilisation data to complete their submissions (as opposed to the minimum 6 weeks specified in the review framework)
- Given the complexity of the required cost-effectiveness submission, a pre-submission meeting between DOH, the evaluators and the affected sponsor should be provided to agree on the scope, applicable populations, comparator(s) and modelling assumptions and inputs.
- A stakeholder forum should be convened as part of this post-market review to discuss and align on assumptions regarding current clinical practice in Australia
- Once the Terms of Reference are ratified by the minister, PBAC minutes related to the discussion and finalisation of the Terms of Reference should be made available to stakeholders

Appendix 1 – PBS eligibility criteria for ezetimibe

Abridged restriction

Ezetimibe and ezetimibe with simvastatin are listed as Authority required (streamlined) pharmaceutical benefits for patients who meet certain criteria. The full restriction wording is available from the PBS website.

Abridged restrictions are provided below with the current streamlined authority codes in brackets.

Ezetimibe

- Treatment of hypercholesterolaemia, in conjunction with dietary therapy and exercise, for co-administration with an HMG CoA reductase inhibitor (statin) in patients whose cholesterol levels are **inadequately controlled with a statin** and who have coronary heart disease (3724), diabetes mellitus (3725), peripheral vascular disease (3726), heterozygous familial hypercholesterolaemia (3727), symptomatic cerebrovascular disease (3728), family history of coronary heart disease (3729), hypertension (3730), are contraindicated to a statin (1989), or where treatment with a statin must be discontinued or reduced because the patient developed a clinically important product related adverse event during treatment with a statin (3731).
- **homozygous sitosterolaemia** (1991).
- patients with **homozygous familial hypercholesterolaemia** who are eligible for PBS-subsidised lipid lowering medication (according to the criteria set out in the General Statement for Lipid Lowering Drugs), in combination with a statin (2438).

Ezetimibe with simvastatin

- Treatment of hypercholesterolaemia, in conjunction with dietary therapy and exercise, in patients whose cholesterol levels are **inadequately controlled with a statin** and who have coronary heart disease (4068), diabetes mellitus (4085), peripheral vascular disease (4086), heterozygous familial hypercholesterolaemia (4069), symptomatic cerebrovascular disease (4096), family history of coronary heart disease (4120), hypertension (4121), or where the patient has developed a clinically important product related adverse event during treatment with a statin necessitating a reduction in the statin dose (4147).
- **homozygous familial hypercholesterolaemia** who are eligible for PBS-subsidised lipid lowering medication (according to the criteria set out in the General Statement for Lipid Lowering Drugs) (4097)

Ezetimibe with atorvastatin (composite pack & FDC)

- Treatment of hypercholesterolaemia, in conjunction with dietary therapy and exercise, in patients whose cholesterol levels are **inadequately controlled with a statin** and who have coronary heart disease (4068), diabetes mellitus (4085), peripheral vascular disease (4086), heterozygous familial hypercholesterolaemia (4069), symptomatic cerebrovascular disease (4096), family history of coronary heart disease (4120), hypertension (4121), or where the patient has developed a clinically important product related adverse event during treatment with a statin necessitating a reduction in the atorvastatin dose (4353).
- **homozygous familial hypercholesterolaemia** who are eligible for PBS-subsidised lipid lowering medication (according to the criteria set out in the General Statement for Lipid Lowering Drugs) (4097)

Ezetimibe with rosuvastatin

- Treatment of hypercholesterolaemia, in conjunction with dietary therapy and exercise, in patients whose cholesterol levels are **inadequately controlled with a statin** and who have coronary heart disease (4068), diabetes mellitus (4085), peripheral vascular disease (4086), heterozygous familial hypercholesterolaemia (4069), symptomatic cerebrovascular disease (4096), family history of coronary heart disease (4120), hypertension (4121), or where the patient has developed a clinically important product related adverse event during treatment with a statin necessitating a reduction in the statin dose (4147).
- **homozygous familial hypercholesterolaemia** who are eligible for PBS-subsidised lipid lowering medication (according to the criteria set out in the General Statement for Lipid Lowering Drugs) (4097)

Inadequate control with a statin is defined as follows:

(1) where the patient falls into a category for which the General Statement for Lipid-Lowering Drugs includes an initial cholesterol threshold for PBS-subsidy (i.e. a patient not in a very high risk category), a cholesterol level in excess of that threshold after at least 3 months of treatment at a maximum tolerated dose of a statin, in conjunction with dietary therapy and exercise; or

(2) where the patient falls into a category for which the General Statement for Lipid-Lowering Drugs allows PBS-subsidised treatment with a statin at any cholesterol level (i.e. a very high risk category patient), a cholesterol level in excess of 4 mmol per L after at least 3 months of treatment at a maximum tolerated dose of a statin, in conjunction with dietary therapy and exercise.

A clinically important product-related adverse event is defined as follows:

(i) Severe myalgia (muscle symptoms without creatine kinase elevation) which is proven to be temporally associated with statin treatment; or
(ii) Myositis (clinically important creatine kinase elevation, with or without muscle symptoms) demonstrated by results twice the upper limit of normal on a single reading or a rising pattern on consecutive measurements and which is unexplained by other causes; or
(iii) Unexplained, persistent elevations of serum transaminases (greater than three times the upper limit of normal) during treatment with a statin
The general statement for lipid lowering drugs is available from the PBS website.

Nurse practitioners can prescribe ezetimibe and its combinations as continuing therapy only, where the treatment of, and prescribing of medicine for, a patients has been initiated by a medical practitioner.