**Pharmaceutical Benefits Scheme**

**Post-market Review**

**Ezetimibe Review**

***Report to the Pharmaceutical Benefits Advisory Committee***

***AUGUST 2017***

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# Abbreviations

| **Abbreviation** | **Full Name / Wording**  |
| --- | --- |
| ACC | American College of Cardiology |
| AHA | American Heart Association |
| ATC | Anatomical Therapeutic Chemical classification |
| BEACH | Bettering the Evaluation and Care of Health |
| BP | Blood pressure |
| CV | Cardiovascular |
| CVD | Cardiovascular disease |
| CPHR | Centre for Population Health Research Deakin University |
| DUSC | Drug Utilisation Sub Committee |
| EAS | European Atherosclerosis Society |
| eGFR | estimated glomerular filtration rate |
| ESC | Economics Sub Committee |
| eTG | Electronic Therapeutic Guidelines |
| FDC | Fixed dose combination |
| FRE | Framingham Risk Equations |
| GSLLD | General Statement for Lipid Lowering Drugs |
| HDL-C | High density lipoprotein |
| ICER | Incremental Cost-Effectiveness Ratio  |
| mg | milligrams |
| LDL-C | Low density lipoprotein |
| mmHg | millimetre of mercury |
| mmol/L | millimoles per litre  |
| NHF | National Heart Foundation |
| NICE | National Institute of Health and Clinical Excellence  |
| NVDPA | National Vascular Disease Prevention Alliance |
| OECD | Organisation for Economic Co-Operation and Development |
| PBAC | Pharmaceutical Benefits Advisory Committee |
| PBS | Pharmaceutical Benefits Scheme |
| QALY | Quality Adjusted Life Year |
| RCT | Randomised controlled trial |
| RPBS | Repatriation Pharmaceutical Benefits Scheme |
| SAND | Supplementary Analysis of Nominated Data |
| SD | Standard deviation |
| TC | Total cholesterol |
| TG | Total triglycerides |
| FDA | United States Food and Drug Administration |

# Glossary

| **Term** | **Explanation** |
| --- | --- |
| Absolute risk | The absolute risk of a disease is the risk of developing the disease over a certain time period. In Australia for the calculation of absolute risk in cardiovascular disease, this time period is usually five years.  |
| Adherence | In this report, an estimate of usage that may inform days of coverage provided by lipid lowering therapy. |
| Algorithm | A process or set of rules to be followed in calculations or other problem-solving operations. |
| ATC C10 | The Anatomical Therapeutic Chemical (ATC) Classification System is used for the [classification](https://en.wikipedia.org/wiki/Drug_class) of [active ingredients](https://en.wikipedia.org/wiki/Medication) of [drugs](https://en.wikipedia.org/wiki/Drug) according to the [organ](https://en.wikipedia.org/wiki/Organ_%28anatomy%29) or [system](https://en.wikipedia.org/wiki/System) on which they act and their [therapeutic](https://en.wikipedia.org/wiki/Therapeutic), [pharmacological](https://en.wikipedia.org/wiki/Pharmacological) and chemical properties. Code ‘C10 Lipid modifying agents’ is a therapeutic subgroup of the Anatomical Therapeutic Chemical Classification System. |
| Cholesterol | A fatty substance that is carried around your body with your blood. Your body produces most cholesterol naturally, with the balance obtained from the diet. Foods vary in their cholesterol content. High concentrations of specific types of cholesterol (e.g. LDL-cholesterol) are associated with cardiovascular disease (CVD).  |
| Co-morbidities | The presence of one or more additional diseases or disorders co-occurring with (that is, concomitant or concurrent with) a primary disease or disorder. |
| Compliance | In this report, prescribing in accordance with the requirements of Pharmaceutical Benefits Scheme restrictions. |
| Co-pack | Pre-packaged combinations of medicines that are convenient to use. |
| Concomitant | Two or more medicines used or given at or almost at the same time (one after the other, on the same day, etc.). |
| Contraindicated | A symptom or condition that is a medical reason for not doing or using something (such as a treatment, procedure, or activity). |
| Dyslipidaemia | An abnormal amount of lipids (e.g. triglycerides, cholesterol and/or fat phospholipids) in the blood. |
| Epidemiology | The study and analysis of the patterns, causes, and effects of health and disease conditions in defined populations. |
| Hepatic | Relating to the liver. |
| HMG CoA reductase inhibitors | A class of lipid-lowering medications, commonly referred to as statins. They inhibit the enzyme HMG-CoA reductase which plays a central role in the body’s production of cholesterol.  |
| Hypercholesterolaemia | An excess of cholesterol in the bloodstream. |
| Intolerance | An inability to eat a food or take a drug without adverse effects. |
| Lipid | Fat-like substances found in your blood and body tissues e.g. triglycerides, cholesterol. |
| Longitudinal study | A research study that involves repeated observations of the same variables (e.g., cholesterol concentration, adverse events) over long periods of time, often many decades. |
| Microalbuminuria | Presence of tiny amounts of albumin (protein) in the urine which may occur in any condition affecting the kidney filters (glomeruli). |
| PBS Statutory pricing | Statutory price reductions, including price disclosure, are provided for in the *National Health Act 1953* (the Act) and the National Health (Pharmaceutical Benefits) Regulations 1960. Statutory price reductions were first introduced through 2007 amendments to the Act. |
| Persistence | In this report, an estimate of usage that may inform duration of treatment.  |
| Pharmacotherapy | Therapy using pharmaceutical medicines, as distinguished from therapy using surgery (surgical therapy), radiation (radiation therapy), movement (physical therapy) etc. |
| Phase III clinical trial | The medicine or treatment is given to large groups of people to confirm its effectiveness, monitor adverse effects, compare it to commonly used treatments, and collect information that will allow the medicine or treatment to be used safely. |
| Phase IV clinical trial | Studies are done after the medicine or treatment has been marketed to gather information on the medicine’s effect in various populations and any adverse effects associated with long-term use. |
| Prevalent | Individuals whose disease developed or was diagnosed before they were identified for the study. |
| Proteinuria | Presence of excess proteins in the urine. |
| Randomised controlled trial | A study in which people are allocated at random (by chance alone) to receive one of two or more clinical interventions. One of these interventions is the standard of comparison or control. The control may be a standard practice, a placebo ("sugar pill"), or no intervention at all. |
| Relative risk | Relative risk is used to compare the risk in two different groups of people. |
| Risk calculator | The Australian Absolute risk calculator combines several risk factors to calculate a risk score (expressed as a percentage), which is a person’s chance of having a CVD event such as a heart attack or stroke in the next five years. |
| Serum | In blood, the serum is the component that is neither a blood cell (serum does not contain white or red blood cells) nor a clotting factor; it is the blood plasma not including the fibrinogens. |
| Sitosterolaemia | A condition in which fatty substances (lipids) from vegetable oils, nuts, and other plant-based foods accumulate in the blood and tissues. These lipids are called plant sterols (or phytosterols). |
| Streamlined authority code | To prescribe a streamlined authority Pharmaceutical Benefits Scheme item, a prescriber is required to include a 'streamlined authority code' on the authority prescription. |
| Titration | The process of gradually adjusting the dose of a medication. There may be up-titration (usually to achieve a target or specific dose) or down-titration (when a high dose is no longer needed or adverse effects have occurred)  |
| Triglycerides | One of a number of fatty substances carried in the blood. A high concentration is associated with heart disease.  |

# Overview

**Background**

In August 2015, the Pharmaceutical Benefits Advisory Committee (PBAC) recommended a Post-market Review of Ezetimibe (the Review). The purpose of the Review was to consider the comparative clinical effectiveness and cost-effectiveness of Pharmaceutical Benefits Scheme (PBS) listed ezetimibe, in the context of the latest available evidence and best clinical practice. The Review was approved by the Minister for Health on 28 September 2015 and after stakeholder submissions and subsequent PBAC consideration, the Terms of Reference (TOR) for the Review were finalised on 24 February, 2016. An independent expert Reference Group was formed to review the information and evidence relating to each TOR and make recommendations to the PBAC on addressing key findings. There were four formal opportunities for public stakeholder consultation during the Review.

**Key findings for each TOR**

1. *Review current utilisation of PBS - listed ezetimibe and ezetimibe combination products. Any review will consider additional data sources that may inform the current utilisation of ezetimibe.*
* Between April 2014 and March 2015, 45,465 people were initiated on PBS-subsidised ezetimibe.
* Analysis of pre and post use of other lipid lowering medicines in the population initiating ezetimibe found that:
* 46% of patients appear to have initiated ezetimibe in accordance with the PBS restriction.
* Between 18.4% and 53.2% of patients initiated ezetimibe in a manner that was not consistent with the PBS restriction.
1. *Review recent clinical guidelines for the treatment of hypercholesterolaemia and compare this to how ezetimibe is currently used on the PBS.*
* A review of the literature identified 11 of the most recent Australian and international clinical treatment guidelines for management of lipid disorders for prevention of cardiovascular disease. All guidelines identified lipid lowering therapy (LLT) as integral to cardiovascular risk reduction.
* Statins are identified as first line therapy by most guidelines, with ezetimibe initiation recommended when additional reduction in low density lipoprotein-cholesterol (LDL-C) is required.
* The General Statement for Lipid Lowering Drugs (GSLLD), used to establish patient eligibility for PBS-subsidised LLT, differs slightly with the Australian clinical treatment guidelines for hypercholesterolaemia (high cholesterol).
* The GSLLD includes target thresholds for commencing lipid lowering therapy and are slightly different to contemporary treatment guidelines. Guidelines now consider a patient’s overall risk of a cardiovascular event rather than lipid levels in isolation as the criteria for prescribing lipid lowering therapy.
1. *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.*
* No clinical trials were identified that reported on patient-relevant outcomes for ezetimibe monotherapy.
* Only one study, IMPROVE-IT, assessed the long-term patient relevant outcomes of ezetimibe added to simvastatin 40mg versus simvastatin 40mg.
* The population in IMPROVE-IT was not considered representative of the current PBS population eligible for subsidised ezetimibe as the study protocol did not allow patients to gradually increase their statin doses to maximally tolerated levels or switch to a higher-potency statin.
* Ezetimibe monotherapy produces a mean 18% reduction in LDL-C compared to a 30%-50% reduction achievable by statins.
* The cost-effectiveness of ezetimibe remains uncertain due to a lack of clinical evidence on long-term patient relevant outcomes.
* An economic model based on the results of the IMPROVE-IT trial would not be suitable for estimating the cost-effectiveness of PBS-subsidised ezetimibe due to differences between the population of the IMPROVE-IT trial and the population eligible to receive PBS-subsidised ezetimibe.

**Outcomes**

The PBAC considered the findings of the Review at its July 2017 meeting. Overall, the PBAC accepted the key findings presented in the Review report.

The PBAC acknowledged the stakeholder comments and recognised the challenges in accurately determining the extent of statin intolerance in the Australian population. However, the PBAC was concerned with the extent of use of ezetimibe outside the PBS restriction and recommended that a price reduction was necessary to restore cost-effectiveness of all subsidised use.

The PBAC agreed that an Authority Required (Streamlined) listing remained the most appropriate restriction to maintain ezetimibe’s place as second line therapy. This restriction is consistent with clinical guidelines and serves to direct use to the high-risk population who will derive most benefit from ezetimibe therapy.

The PBAC made a number of other recommendations in its advice to the Minister. These included the removal of the General Statement on Lipid Lowering Drugs, due to its inconsistency with current guidelines and Quality Use of Medicine initiatives to ensure optimal first line initiation and gradual increase of statin therapy to maximally tolerated doses.

# Executive Summary

Large numbers of Australians have high cholesterol. High cholesterol is a major risk factor for coronary heart disease, stroke and peripheral vascular disease. Ezetimibe is a medicine used to lower cholesterol with the goal of reducing the occurrence of cardiovascular events such as heart attacks and stroke. Ezetimibe is listed on the Pharmaceutical Benefits Scheme (PBS) for the treatment of high cholesterol in certain patient populations.

The Post-market Review of Ezetimibe has been conducted as part of the Australian Government’s post-market monitoring program. The program aims to ensure the continued safe, cost-effective and quality use of medicines listed on the PBS. The purpose of this Review was to consider the comparative clinical effectiveness, ‘value for money’, and financial cost of ezetimibe to the PBS, in the context of the latest available evidence and best clinical practice.

In 2003, the Pharmaceutical Benefits Advisory Committee (PBAC) first recommended the PBS listing of ezetimibe based on a comparison of data on lipid concentrations available at the time. There were no long-term studies available to assess whether reduction of lipid concentrations with ezetimibe resulted in fewer cardiovascular events. In contrast, for the 3-hydroxy-3methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, there was a great body of evidence to show that they reduced low density lipoprotein cholesterol (LDL-C) serum concentrations, which translated to a lower risk of cardiovascular events and mortality.

By November 2013, there were a number of ezetimibe with statin combination products listed on the PBS. The PBAC expressed concern that the listing of combination ezetimibe and statin products (co-packs and fixed dose combinations) on the PBS may direct use away from optimal dose titration of statins. The PBAC also noted at the time that there were no studies reporting long-term patient relevant outcome data for ezetimibe, and that PBS expenditure on the medicine was high. The PBAC recommended a Post-market Review (PMR) of Ezetimibe in August 2015 and the Minister for Health agreed to the Review in September 2015.

The PMR of Ezetimibe addressed the following three Terms of Reference:

1. 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.
2. Review recent clinical guidelines for the treatment of hypercholesterolaemia and compare this to how ezetimibe is currently used on the PBS.
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.

An independent expert Reference Group guided and provided advice to the Review. There were a number of opportunities for stakeholder consultation and input throughout the Review.

## Term of Reference 1: 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.**

An utilisation analysis of unit record level PBS data (including under co-payment prescriptions) was undertaken to answer the following research question in 2016 (December 2016 Analysis – **Appendix E**):

“Is ezetimibe being prescribed on the PBS in accordance with the PBS restrictions for ezetimibe, which require titration of statins to maximally tolerated doses before initiation of treatment with ezetimibe?”

Certain restrictions or conditions may apply to PBS-listed medicines to ensure the medicine is subsidised in situations where treatment is proven to be clinically effective and cost-effective. For most patients, the PBS restrictions for ezetimibe require titration of statins to maximally tolerated doses before starting treatment with ezetimibe. This is to ensure patients receive the maximum benefit possible from the statin medicine prior to adding or switching to ezetimibe therapy.

The December 2016 Analysis identified all patients who commenced ezetimibe between April 2014 and March 2015. A total of 45,645 patients initiated ezetimibe during this period, of whom 6,938 (Cohort 1) had no prior lipid lowering therapy (LLT) within the previous 24 months, and 38,707 (Cohort 2) had at least one dispensing of a lipid lowering medicine in the prior 24 months.

These data suggest the majority of prescribers broadly comply with the PBS restriction for ezetimibe. A high proportion (82.7%) of all patients starting ezetimibe had at least one dispensing record for a statin in the previous two years. A small percentage (2.3%) had prior exposure to non-statin LLT before commencing ezetimibe, and the remaining 15.2% of patients had no prior exposure to statins or other LLT in the 24 months prior to their first dispensing of ezetimibe. A longer look back period may detect earlier dispensing of LLT medicines for some patients, but would be less relevant for the current review.

There may be legitimate clinical circumstances that account for the absence of prior statin use in new users of ezetimibe. For example, where a patient had experienced a major adverse event from taking statins more than two years ago and subsequently avoided all LLT for this period.

From the December 2016 Analysis, there was evidence to suggest that approximately 30% of patients with a prior history of statin use had titrated their statin dose, either up or down. This may reflect titration to further lower their LDL-C concentrations or in response to adverse effects. For patients who remained on the same dose of statin, the PBS data are insufficiently detailed to demonstrate that they were not already on the maximum tolerated dose of statin. There may be both legitimate and non-legitimate clinical circumstances that account for the absence of statin titration in PBS data. For example, patients may have already been optimally titrated to statins prior to the study period. Alternatively, as some stakeholder submissions also suggested, prescribers add ezetimibe to statin therapy to avoid perceived adverse effects of higher dose statins.

Despite these caveats, the December 2016 Analysis reported that 15.9% of ezetimibe use was unlikely to be prescribed in accordance with the PBS restrictions. Another finding from the December 2016 Analysis was that a significant proportion of ezetimibe initiators did not continue receiving prescriptions for LLT, including ezetimibe, in the 6-12 months post initiation of ezetimibe. Discontinuation of all LLT was higher for individuals with no previous LLT (44%) than those with previous LLT (11.6%). The difference in persistence to LLT between the two groups may be due to the underlying patient characteristics of each group. Patients with a prior statin history may be accustomed to taking medication, unlike those without a prior statin history. While the December 2016 Analysis suggests poor persistence to therapy, the Reference Group acknowledged the Drug Utilisation Sub Committee (DUSC) advice that these studies were not specifically designed to measure adherence or persistence. However, the DUSC agreed that new users of medicines are likely to be at higher risk of non-adherence and non-persistence.

The Reference Group also noted from recent literature, that patients who take less than 80% of their prescribed statin regimen have a 45% relative increase in total mortality compared with more adherent patients, an increase greater than that observed with poor adherence to many other cardiac drugs.[[1]](#endnote-2) This underlines the importance of patient education when initiating or recommencing LLT, in order to ensure patients adhere to LLT over the long-term to achieve a sustained reduction in cardiovascular risk.

The DUSC reviewed the December 2016 Analysis in February 2017 and was concerned with the approach taken to answer the utilisation research question for Term of Reference 1. The DUSC noted that the December 2016 Analysis had not linked all LLT utilisation pre and post ezetimibe initiation at the individual patient level and that this was likely to have underestimated the number of patients who were not using ezetimibe in accordance with the PBS restrictions. The DUSC noted that for some patients, there was strong evidence which supported compliance (denoted in green, below) or non-compliance (denoted in red, below) with PBS restrictions. The DUSC also noted there was uncertainty for some patients as to whether their ezetimibe use was in accordance with the PBS restrictions due to insufficient information being available in PBS data. These initiators were placed in a separate ‘uncertain’ category (denoted in orange, below).

In summary, DUSC proposed that new users of ezetimibe could be categorised into the following three groups (March 2017 Analysis - **Appendix E**):

• those initiating ezetimibe in accordance with the PBS restrictions (green);

• those initiating ezetimibe in a manner that is not consistent with the PBS restrictions (red); and

• the remainder for whom compliance with the PBS restriction is unknown (orange).

The March 2017 Analysis was conducted using the same dataset and the same Cohorts (1 and 2) as identified in the December 2016 Analysis.

The March 2017 Analysis found that 46.9 % of patients were in the ‘green’ group described above, 18.4% of patients were in the ‘red’ group, and 34.8% of patients were in the ‘orange’ group.

Taking the results of the March 2017 Analysis into account, the Reference Group considered the estimate of ezetimibe use outside the PBS restrictions would fall somewhere in the range of 18.4% - 53.2% (i.e. the proportions of use categorised as red and orange). The Reference Group acknowledged that this is a best estimate due to the limitations of PBS data. Ezetimibe use that does not appear to comply with the PBS restrictions may in some cases be clinically appropriate; however, is unlikely to be cost-effective.

The Reference Group also suggested that for the 18.4% – 53.2 % of patients who use ezetimibe outside the PBS restriction, placebo is not the appropriate comparator for a cost-effective analysis. The comparator for this group of patients should be a higher dose of statin or switching to a higher potency statin.

### Review advice to the PBAC

1. There is a need for greater education of prescribers on the importance of adherence to the PBS restrictions to promote optimal and cost-effective use of subsidised LLT. Results of the March 2017 Analysis indicate the estimate of ezetimibe use that is not consistent with the PBS restriction, would fall somewhere in the range of 18.4% - 53.2%.

The PBAC may wish to recommend a price reduction for ezetimibe, for a proportion of use within the range of 18.4% - 53.2% where the appropriate comparator should be higher dose statin or switching to a higher potency statin.

1. The December 2016 Analysis of PBS data suggests that poor persistence is an issue when patients are commencing or recommencing LLT. The literature also suggests poor adherence and persistence is a concern, as patients who are less adherent to statin therapy have a significantly increased risk of death compared to those who are more adherent to statins. The Reference Group considered this is a quality use of medicines issue which could potentially be addressed through both prescriber and patient education.

The PBAC may wish to request that future education programs reinforce and promote:

* the importance of adherence and persistence with LLT to reduce cardiovascular risk, particularly in new users of chronic medicines; and
* use of statins first line at the maximum tolerated dose for optimal LDL-C reduction and management of cardiovascular risk.

## Term of Reference 2: Clinical guidelines and PBS restrictions

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

The most recent Australian and international clinical treatment guidelines for management of metabolic lipid disorders to prevent cardiovascular outcomes were reviewed. All current guidelines for primary prevention of cardiovascular disease (CVD) recommend treatment based on an individual patient’s risk of having a future cardiovascular event. For secondary prevention of CVD (i.e. patients with pre-existing CVD), a high risk status is applied categorically rather than assessed using a risk calculator. The variation between Australian and international guidelines reflects differences in absolute risk thresholds in each country and the approach to pharmacotherapy.

All guidelines recommend the use of statins as first line pharmacotherapy to lower LDL-C concentrations. This is due to the quality and quantity of clinical evidence available that lowering LDL-C through the use of statins translates to a reduction in risk of cardiovascular events. The guidelines place ezetimibe after statins due to the limited patient outcome data available. There is only one trial, IMPROVE-IT,[[2]](#endnote-3) showing that a reduction in LDL-C through the use of ezetimibe combined with a statin translates to a reduced risk of cardiovascular events. However, there was no significant overall effect on mortality in this trial.

Recent literature suggests that significant benefit from ezetimibe is restricted to those with high risk of cardiovascular events in a secondary prevention population.[[3]](#endnote-4),[[4]](#endnote-5) During the seven years of IMPROVE-IT, patients with prior coronary artery bypass surgery (CABG) received significantly greater benefit from treatment with ezetimibe in addition to simvastatin compared to those without prior CABG (absolute risk reduction of 8.8% versus 1.3%). The Bohula et al[[5]](#endnote-6)  analysis of the IMPROVE-IT trial found those who showed a significant benefit from ezetimibe plus statin therapy over statin monotherapy had three or more additional risk factors. Low risk patients (nil to one risk factor) showed no benefit from the addition of ezetimibe. This underlines the importance of restricting PBS subsidised use of ezetimibe to the high risk population.

S[ection 101](http://www.austlii.edu.au/au/legis/cth/consol_act/nha1953147/s101.html) of the *National Health Act 1953* *(Commonwealth)* requires the PBAC to consider both the cost and clinical effectiveness of a medicine compared with other treatments for the same condition. PBS restrictions reflect the outcomes of the PBAC’s cost-effectiveness deliberations whereas clinical guidelines do not explicitly consider cost-effectiveness. Consequently, PBS restrictions and clinical guidelines do not always align.

The General Statement for Lipid Lowering Drugs[[6]](#endnote-7) (GSLLD) forms part of the restrictions for PBS subsidised statins, fenofibrate and gemfibrozil. A comparison of the GSLLD and Australian treatment guidelines, *Guidelines for the Management of Absolute Cardiovascular Disease Risk* (National Vascular Disease Prevention Alliance, 2012 (NVDPA-2012)), found both guidelines to be broadly consistent in terms of the risk factors that are considered prior to recommending commencement of LLT. The Reference Group considered that there is general prescribing compliance with the GSLLD. However, the GSLLD no longer reflects contemporary use of LLT and could be removed. For example, for primary prevention, most clinicians would commence patients on a LLT at total cholesterol concentrations lower than 9 mmol/L, which is currently the threshold in the GSLLD for patients not otherwise included in specific clinical categories.

In considering the report in February 2017, the DUSC advised that the statin market is mature but the ezetimibe market had not yet stabilised. Ezetimibe use is predominantly ‘add on’ to statins, but in up to half the PBS population prescribed ezetimibe, it is uncertain whether statins have been trialled at maximum tolerated doses before ezetimibe is prescribed. The Reference Group therefore considered PBS subsidised statins could become unrestricted and ezetimibe should remain Authority Required (Streamlined).

### Review advice to the PBAC

1. The use of LLT is now an established approach to reduce cardiovascular risk. The PBAC may wish to consider removal of the GSLLD from the PBS restriction for statins, fenofibrate and gemfibrozil. Removal of the GSSLD will require revision of the ezetimibe PBS restriction wording.
2. The current PBS restrictions for statins are 15 years old. Together with the reduction in statin price achieved through PBS Statutory Pricing policy, the Reference Group recommends the PBAC consider derestriction of statins from Restricted Benefit to Unrestricted Benefit.
3. The Reference Group recommends the PBAC consider the place of ezetimibe remain confined to second line, compatible with clinical guidelines, via an Authority Required (Streamlined) listing.
4. The PBAC may wish to consider revising the restriction for ezetimibe as displayed below (refer below for an abbreviated version, further details found in section 2.4). Implementation will require prescriber education to promote the importance of absolute risk reduction in the approach to cardiovascular disease management. In the future, the PBAC may wish to apply a contemporary absolute risk threshold approach to the ezetimibe restriction for both the high and low cardiovascular risk populations.

Revised ezetimibe PBS restriction for PBAC consideration

**Authority Required (Streamlined)**

**Hypercholesterolaemia**

* **Clinical Criteria**
	+ The treatment must be co-administered with an HMG CoA reductase inhibitor (statin),

**AND**

* + Patient must have cholesterol concentrations that are inadequately controlled with an HMG CoA reductase inhibitor (statin). Inadequate control is a cholesterol concentration in excess of 4mmol/L after at least 3 months of treatment at a maximum tolerated dose of a statin. The dose and duration of statin treatment and the cholesterol concentration which shows inadequate control must be documented in the patient’s medical records when ezetimibe is initiated,

**AND**

* + Patient falls into at least one of the very high risk categories described as:
		1. coronary heart disease which has become symptomatic
		2. cerebrovascular disease which has become symptomatic
		3. peripheral vascular disease which has become symptomatic
		4. diabetes mellitus with microalbuminuria (defined as urinary albumin excretion rate of >20mcg/min or urinary albumin to creatinine ratio of > 2.5 for males, > 3.5 for females)
		5. diabetes mellitus in Aboriginal or Torres Strait Islander patients
		6. diabetes mellitus in patients aged 60 years or more
		7. family history of coronary heart disease which has become symptomatic before the age of 55 years in two or more first degree relatives
		8. family history of coronary heart disease which has become symptomatic before the age of 45 years in one or more first degree relatives
		9. heterozygous/homozygous familial hypercholesterolaemia.

**OR**

* + Where a patient’s level of absolute risk of a cardiovascular event is greater than 15% over 5 years as calculated by the Australian Absolute Cardiovascular Disease Risk Calculator (National Vascular Disease Prevention Alliance).
* **Clinical Criteria**
	+ Homozygous sitosterolaemia.
* **Clinical Criteria**
	+ Patient must be one in whom treatment with an HMG CoA reductase inhibitor (statin) is contraindicated.
* **Clinical Criteria**
	+ Patient must have developed a clinically important product-related adverse event during treatment with an HMG CoA reductase inhibitor (statin) necessitating a reduction in the statin dose. The type and severity of the adverse event must be documented in the patient’s medical records.

**OR**

* + Patient must have developed a clinically important product-related adverse event during treatment with an HMG CoA reductase inhibitor (statin) necessitating a withdrawal of the statin treatment. The type and severity of the adverse event must be documented in the patient’s medical records.

## Term of Reference 3: Recent evidence and review of cost-effectiveness

**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.**

An extensive literature review sought to identify recent clinical studies of ezetimibe reporting on long-term patient relevant outcomes. Only one study met the review selection criteria to assess whether the addition of ezetimibe to a statin is associated with superior long-term patient outcomes. IMPROVE-IT[[7]](#endnote-8) was a secondary prevention study that assessed long-term patient outcomes associated with the addition of ezetimibe to simvastatin. In the absence of better evidence on the long-term outcomes of the use of ezetimibe in the population with hypercholesterolaemia, the outcomes of the IMPROVE-IT trial were considered alongside other evidence included in the analysis of clinical effectiveness.

The Reference Group expressed confidence that for patients receiving ezetimibe, the clinical outcomes of IMPROVE-IT confirm the acceptability of the absolute reduction in LDL-C as a valid surrogate for the reduction of the relative risk of major vascular events. The reduction in cardiovascular event rate was as predicted by the known relationship between absolute reduction in LDL-C and the relative risk reduction. IMPROVE-IT demonstrated a risk reduction in a primary composite endpoint (cardiovascular death, major coronary event or non-fatal stroke); however, there was no significant overall effect on mortality alone. There is also no apparent safety issue associated with long-term use of ezetimibe.

Long-term patient outcomes reported in the IMPROVE-IT trial may not be fully generalisable to the target Australian population. The IMPROVE-IT study enrolled a trial population which did not meet the PBS eligibility criteria for subsidised prescription of ezetimibe. Participants were restricted to the secondary prevention population and were treated with a constant dose of simvastatin. There was no up-titration to maximally tolerated doses of statins or switch to statins of higher potency, as required by the current PBS restriction for ezetimibe. Participants LDL-C concentrations ranged between 1.3 and 2.43 mmol/L, whereas high risk patients can access PBS subsidised LLT under the GSLLD at any cholesterol concentration.

As described under Term of Reference 2, recently published literature reporting on sub-group analyses of the IMPROVE-IT study suggests that any benefit of ezetimibe is restricted to those with high risk in a secondary prevention population[[8]](#endnote-9),[[9]](#endnote-10),[[10]](#endnote-11),[[11]](#endnote-12).

On the basis of the published evidence, the Reference Group accepted that a reduction in LDL-C correlates with the reduction of cardiovascular risk, however the reduction is likely to be of more benefit in higher risk patients. To achieve the largest reduction in LDL-C in the majority of cases, the initial use of statins should be promoted with up-titration to the maximum tolerated dose or switch to statin of higher potency prior to the introduction of ezetimibe. The quality and quantity of evidence for preventing cardiovascular events with statins is stronger and the percentage reduction in LDL-C with statins is greater than with ezetimibe. Therefore, the PBS restrictions placing ezetimibe as a second line non-statin LLT option should remain.

Application of the evidence reporting on long-term patient relevant outcomes casts uncertainty about the cost-effectiveness of ezetimibe in combination with statin versus statin monotherapy. The Reference Group agreed that the results of the economic evaluations previously considered by the PBAC and those re-presented in a submission to the post-market review, seem to overestimate the incremental long-term benefits associated with a combination of ezetimibe and a statin.

The structure of the economic model provided by the sponsor to the Review is unchanged from past submissions to the PBAC and therefore concerns remain related to: the risk equations used to transform the reduction in lipid concentrations to final outcomes, the long cycle length (1 year) and model time horizon (70 years).

The Reference Group considered that a large proportion of patients using ezetimibe as second line therapy would be older than 50 years and requested an additional analysis be conducted on the time horizon at ten year intervals between 10 years and 70 years.

The results of this sensitivity analysis show that the Incremental Cost-Effectiveness Ratios (ICERs) estimated as either a cost/life year gained (LYG) or cost/quality-adjusted life year (QALY) remain unchanged when the time horizons extended beyond 30 years (**Appendix J**, Table 1.3, p.20). After the first 30 cycles (years) of the Markov model, the survival rate is zero and there is no difference in either the incremental costs or the outcomes.

The Reference Group noted the sensitivity of the ICER to the efficacy estimates as well as the time horizon. The efficacy estimates provided by the sponsor were based on a meta-analysis conducted in 2006, that was not updated for the more recently published evidence and might have overestimated the efficacy [reduction in Total Cholesterol (TC): High Density Lipoprotein (HDL) ratio of -19.5% vs -2.6% in the ezetimibe and comparator arms, respectively] of ezetimibe added to statin versus statin monotherapy. During the Review, alternative efficacy estimates were obtained from a meta-analysis of trials that enrolled primary, secondary or mixed prevention populations, all receiving second line treatment with ezetimibe plus statin (intervention) versus up-titrated statin (control). This *ad hoc* meta-analysis was conducted by the Deakin Health Economics team for the sensitivity analysis of the modelled economic evaluation presented by the sponsor (MSD) in the 2016 submission for the Review (**see Appendix J**, p.21, Table 1.4 footnotes for the list of trials). The ICER was found to be sensitive to the variation in efficacy estimates. Reduction in TC: HDL ratios of -18.84% versus -9.65% in the intervention and comparator arms, respectively, produced ICER estimates that almost double across all time periods in comparison to the ICER estimates based on the TC:HDL ratios presented in the MSD submission (**Appendix J**, Figure 1.2.4 , p.22).

The Reference Group noted the Economics Sub Committee (ESC) advice that due to applicability issues an economic model based on the results of IMPROVE-IT would not provide a more reasonable estimate of the cost-effectiveness of current ezetimibe use on the PBS.

Current use of ezetimibe in patients who have not received maximally tolerated doses of statins may be clinically appropriate but has not been shown to be cost-effective. The PBAC has considered economic evaluations for ezetimibe where the comparator is a non-statin LLT or placebo. In considering the current cost-effectiveness of ezetimibe, the Reference Group agreed that for a proportion of use in the range 18% - 53.2%, the appropriate comparator would be maximum tolerated doses of statin or switching to a statin of higher potency.

Therefore, a weighted comparison with a proportion of use compared to up-titration of statin dose/switching to a higher potency statin and a proportion of use compared to placebo/non statin LLT may be one way to estimate the cost-effectiveness of ezetimibe in current practice.

### Review advice to the PBAC

1. Recent literature suggests significant benefit from ezetimibe is restricted to those patients in the highest category of cardiovascular risk and the magnitude of LDL-C reduction is smaller than that achieved by statins. This underlines the importance of restricting use of ezetimibe to second line following optimal use of statins and in those patients with very high risk.
2. The base case ICER presented in the sponsor’s submission is considered uncertain. This is because the approach used for extrapolating the benefits beyond the period of the trial follow-up is likely to have overestimated the incremental long-term benefits associated with a combination of ezetimibe and a statin.
3. The evidence reporting on long-term patient relevant outcomes casts uncertainty over the cost-effectiveness of ezetimibe in combination with statin versus statin monotherapy. This arises from the variability in estimates of clinical efficacy in terms of the TC:HDL ratio. Results of the economic evaluations previously considered by the PBAC and provided by the sponsor during the Review (including the sponsor’s model proposed to the Review versus the IMPROVE-IT trial outcomes) seem to overestimate the incremental long-term benefits associated with a combination of ezetimibe and a statin.
4. An economic model based on the results of the IMPROVE-IT trial would not provide a reasonable estimate of the cost-effectiveness of current ezetimibe use on the PBS due to applicability issues.
5. The Reference Group agreed, in considering the cost-effectiveness of ezetimibe, the comparators include:
	1. placebo/non statin LLT for those patients contraindicated to statins; and
	2. up-titration of statin to maximum tolerated dose/switching to a higher potency statin.

# Report Structure

This Report contains a background chapter and three separate sections to address each of the Terms of Reference. Updates to this report following PBAC sub-committee consideration, Reference Group consideration, and stakeholder comments, have been included within the body of this report.

**Background**

Provides the context for post-market reviews, background information on the Ezetimibe Post-market Review, an explanation of dyslipidaemia as a risk factor for cardiovascular disease and background on assessment of cardiovascular disease risk.

**Section 1 – Term of Reference 1**

Review current utilisation of Pharmaceutical Benefits Scheme (PBS)–listed ezetimibe and ezetimibe combination products.

Provides key findings, a summary of the utilisation analysis, key issues raised by stakeholders and Reference Group advice.

**Section 2 – Term of Reference 2**

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

Provides key findings, a summary of the published evidence, key issues raised by stakeholders and Reference Group advice.

**Section 3 – Term of Reference 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.

Provides key findings, a summary of the published evidence, key issues raised by stakeholders and Reference Group advice.

# Background

## B.1 Context for a post-market review

The Australian Government has introduced a systematic post-market approach to monitoring medicines subsidised under the Pharmaceutical Benefits Scheme (PBS) to inform decision making at all levels throughout the medicine listing cycle (from the registration of a medicine right through to its use by consumers). PMRs fall under the quality use of medicines objective of the National Medicines Policy framework.  It is important for the Government to continue to monitor clinical and cost-effectiveness of medicines after listing on the PBS. Reviews of cost-effectiveness ensure that the cost of medicines to the PBS appropriately reflects health outcomes expected, that there is quality use of PBS-listed medicines, and that ongoing sustainability of the PBS is achieved.

### B.1.1 National Medicines Policy (NMP)

The National Medicines Policy (NMP) provides a broad framework that aims to ensure improved health outcomes for all Australians through access to and appropriate use of medicines.

The four central objectives of the policy are:

* timely and affordable access to medicines for all Australians
* appropriate standards of quality, safety, and efficacy of medicines
* quality use of medicines
* maintenance of a responsible and viable medicines industry in Australia.

A PMR is one mechanism that contributes to ensuring the quality use of PBS-listed medicines.

*Quality use of medicines* is defined as:

* selecting management options wisely
* choosing suitable medicines if a medicine is considered necessary
* using medicines safely and effectively.

The definition of quality use of medicines applies equally to decisions about medicine use by individuals and decisions that affect the health of the population.

### B.1.2 Australian Commission on Safety and Quality in Health Care (ACSQHC)

The ACSQHC was established to lead and coordinate national improvements in the safety and quality of health care[[12]](#endnote-13). PMRs contribute to the stated goals and standards of the ACSQHC, primarily through goal three and standard two which focus on partnering with consumers in planning, designing and evaluating health care.

PMRs achieve this by providing multiple opportunities for consumers, and other stakeholders, to provide input into the review, via public consultation and through the consumer advocate who is appointed as part of the review reference group.

### B.1.3 Pharmaceutical Benefits Scheme (PBS)

The PBS provides reliable, timely and affordable access to a wide range of medicines for all Australians. Under the PBS, the Australian Government subsidises the cost of listed medicines to help people afford prescription medicines for most medical conditions.

### B.1.4 Pharmaceutical Benefits Advisory Committee (PBAC)

The PBAC is an independent expert body appointed by the Australian Government. The members of the PBAC are health professionals (medical practitioners and pharmacists), health economists and consumer representatives. The PBAC meets three times a year, usually in March, July and November.

The PBAC has statutory functions under the *National Health Act* *1953*, to make recommendations to the Minister for Health (the Minister) on what medicines are to be listed on the PBS and to advise the Minister on any matters concerning the operation of the PBS.

In making recommendations to list medicines on the PBS, the PBAC appraises the evidence for comparative clinical effectiveness, cost-effectiveness and financial cost of each medicine compared to other medicines and treatments currently available in Australia[[13]](#endnote-14).

In addition to making a recommendation to list a medicine on the PBS, the PBAC may also review the medicine after it has been listed for safety, comparative clinical effectiveness and cost-effectiveness, its utilisation and financial cost. It is important to monitor clinical and cost-effectiveness of medicines to ensure that the cost to the PBS appropriately reflects the health outcomes expected. The PBAC advises the Minister on the need for, and provides recommendations on, post-market reviews[[14]](#endnote-15).

The PBAC has two sub-committees to assist with analysis and advice: the Drug Utilisation Sub Committee (DUSC) and the Economics Sub Committee (ESC).

The DUSC has a role in the review of utilisation of PBS-listed medicines. The DUSC assesses estimates on projected usage and financial cost for medicines. It also collects and analyses data on actual use in the clinical setting (including in comparison with different countries), and provides this advice to the PBAC.

The ESC assesses clinical and economic evaluations of medicines submitted to the PBAC for listing, and advises PBAC on the technical aspects of these evaluations.

Information relating to the PBS, and the PBAC, DUSC and ESC meeting dates, agendas and outcomes are available on the [PBS website](http://www.pbs.gov.au/pbs/home)[[15]](#endnote-16).

### B.1.5 Post-market monitoring

The PMR program enables a methodological, systematic and transparent approach to reviewing medicines subsidised by the PBS. PMRs were initiated under the 2011‑12 Budget measure ‘*Improving sustainability of the PBS through enhanced post-market surveillance’.*

The PMR program aims to contribute to:

* Improved patient safety through better understanding of adverse events and medicine-related harms, including hospitalisations.
* A more sustainable PBS through better targeting of medicines, and avoidance of preventable wastage, or inappropriate prescribing.
* A better knowledge base to understand medicines utilisation, to validate the intended clinical benefit which will inform medicines evaluation processes.
* A strengthened approach to medicine pricing management, including through better management of clinical and economic uncertainty.
* Overall improvements to the quality use of medicines and education for patients and prescribers.

The Minister may initiate a PMR, usually as a result of a recommendation from the PBAC, when concerns are raised relating to one or more of the following: the quality use of a medicine; cost-effectiveness; comparative clinical effectiveness; comparative safety; and unexpected patterns of utilisation. The agreed framework, *PBS Post-market Reviews March 2015*, outlines the usual approach to PMRs and is available on the PBS website[[16]](#endnote-17).

## B.2 Overview of the Review Process

The PMR process is detailed on the [PMR website](http://www.pbs.gov.au/info/reviews/subsidised-medicines-reviews/). The key dates for the PMR of Ezetimibe are available at **Appendix C.**

In accordance with the framework, the Review consisted of:

* establishment of draft Terms of Reference (TOR) by the PBAC and direction to commence the review by the Minister
* stakeholder consultation on the draft TOR
* review of stakeholder comments on the draft TOR by the PBAC and ratification of the final TOR
* establishment of a Reference Group to guide the Review
* engagement of independent external evaluators
* undertaking a stakeholder forum to inform and engage with a wide range of stakeholders as recommended by the Reference Group
* preparation and publication of a report including all evidence prepared by evaluators and other materials considered by the Reference Group
* opportunity for all stakeholders to provide additional comments
* finalisation of the report.

The final Review report was provided to the PBAC. The PBAC considered the report and formed recommendations for the Minister. Following consideration by the Minister, the final report was published on the [Ezetimibe Review website](http://www.pbs.gov.au/info/reviews/post-market-review-ezetimibe).

### B.2.1 Review Reference Group

A Reference Group was formed to assist in the review of the evidence and information for each of the Review’s TOR, and to ensure that the perspectives of stakeholders were considered in the preparation of the final report to the PBAC. The Reference Group provided the PBAC with options and advice to address key findings. Members of the Reference Group were appointed as either individuals or organisational representatives. Representation included clinical experts, health economists, and representatives of relevant health professional and consumer organisations. The Reference Group for the Ezetimibe Review was appointed on 8 April 2016. A full list of Reference Group members is at **Appendix D**.

### B.2.2 Report Sources

The Review report was compiled from a wide range of sources including scientific literature, data analysis and stakeholder input.

All material prepared by the external evaluation group and the Reference Group has no redacted information and is publicly accessible. However, some stakeholders may have requested that their submission to the Review, or details of the person or organisations making the submission, remain confidential.

## B.3 About the Ezetimibe Post-market Review

The PBAC first recommended listing ezetimibe (Ezetrol®) on the PBS in June 2003, based on a comparison of data on lipid concentrations which was available at the time. Longer term studies to assess whether reduction of lipid concentrations by ezetimibe actually resulted in fewer cardiovascular events were not available. A summary of the PBS listing history of ezetimibe and its combination products is at **Appendix A**.

Ezetimibe is one of a group of medicines called lipid modifying agents. The most commonly used lipid modifying agents are HMG-CoA reductase inhibitors, or statins.

Ezetimibe inhibits the absorption of dietary and biliary cholesterol and related plant sterols from the small intestine. This reduces delivery of cholesterol to the liver, decreasing cholesterol stores in the liver and increasing hepatic uptake of cholesterol from the blood[[17]](#endnote-18). In contrast, HMG-CoA reductase inhibitors, or statins, act by inhibiting cholesterol synthesis in the liver.

Lipid lowering agents (statins, ezetimibe, fenofibrate and gemfibrozil) are listed on the PBS for use in patients who meet the criteria set out in the General Statement for Lipid-Lowering Drugs (GSLLD). This statement is based on an approach to the absolute cardiovascular risk to patients, taking into account the presence of certain co-morbidities and total and/or HDL cholesterol or triglyceride values.

Ezetimibe is listed on the PBS for the treatment of high cholesterol in certain patient populations. The goal of treatment is a reduction in the risk of cardiovascular events such as heart attacks and stroke. However, additional restrictions apply to the PBS prescribing of ezetimibe including: a) a requirement that unless patients are contraindicated or intolerant of statins, ezetimibe must be co-administered with a statin; and b) patients must have cholesterol concentrations that are inadequately controlled with a statin and suffer from a defined comorbid condition (coronary heart disease, diabetes mellitus, peripheral vascular disease, heterozygous familial hypercholesterolaemia, symptomatic cerebrovascular disease, family history of coronary heart disease, or hypertension).

The abbreviated restriction criteria used to determine patient eligibility for subsidy is in Table 1, while the full restrictions are at **Appendix B**.

Table 1: PBS prescribing restrictions for ezetimibe (abbreviated)

| **Medicine** | **PBS Restrictions** |
| --- | --- |
| **Monotherapy*** Ezetimibe
 | **Authority Required (STREAMLINED)**Patient must meet the criteria set out in the General Statement for Lipid-Lowering Drugs **AND**The treatment must be in conjunction with dietary therapy and exercise,**AND**The treatment must be co-administered with an HMG CoA reductase inhibitor (statin),**AND**Patient must have cholesterol concentrations that are inadequately controlled with an HMG CoA reductase inhibitor (statin), **AND**Patient must have one (or more) of the following: * diabetes mellitus
* family history of coronary heart disease
* peripheral vascular disease
* heterozygous/homozygous familial hypercholesterolaemia
* symptomatic cerebrovascular disease
* hypertension
 |
| **Authority Required (STREAMLINED)**Homozygous sitosterolaemia |
| **Authority Required (STREAMLINED)**Patient must meet the criteria set out in the General Statement for Lipid-Lowering Drugs **AND**statins are contra-indicated**or**patient has developed a clinically important product related adverse drug event necessitating withdrawal of statin treatment**or**patient has developed a clinically important product related adverse drug event necessitating a reduction in statin dose |
| **Combination Therapy*** Ezetimibe plus Atorvastatin
* Ezetimibe plus Simvastatin
* Ezetimibe plus Rosuvastatin
 | **Authority Required (STREAMLINED)**Patient must meet the criteria set out in the General Statement for Lipid-Lowering Drugs **AND**The treatment must be in conjunction with dietary therapy and exercise,**AND**Patient must have cholesterol concentrations that are inadequately controlled with an HMG CoA reductase inhibitor (statin), **AND**Patient must have one (or more) of the following: * + diabetes mellitus
	+ family history of coronary heart disease
	+ peripheral vascular disease
	+ heterozygous/homozygous familial hypercholesterolaemia
	+ symptomatic cerebrovascular disease
	+ hypertension
 |
| **Combination Therapy*** Ezetimibe plus Atorvastatin 10/10 mg
* Ezetimibe plus Simvastatin 10/10 mg, 10/20 mg
* Ezetimibe plus Rosuvastatin 5/10 mg
 | **Authority Required (STREAMLINED)**Patient must meet the criteria set out in the General Statement for Lipid-Lowering Drugs **AND**Patient has developed a clinically important product related adverse drug event necessitating a reduction in statin dose |

### B.3.1 Why review ezetimibe?

In July 2013, the PBAC expressed concern that the listing of the ezetimibe plus atorvastatin co-pack may direct use away from the optimal titration of statin monotherapy. Optimal titration of statins refers to the process of gradually adjusting the dose of a statin or prescribing a statin of higher potency until the maximum (or targeted) reduction in LDL-C concentration is achieved. Dose adjustments and choice of statin are balanced against any adverse effects that may occur.

In November 2013, the PBAC again expressed concern when considering the listing of the ezetimibe plus rosuvastatin co-pack. The PBAC noted at that time that there were no studies of ezetimibe with patient relevant outcome data, such as reduction in cardiovascular events or stroke or improved mortality. However, outcome studies had been undertaken for a number of statin medicines.

There has been a significant reduction in the PBS price of statins since 2003 through PBS Statutory Pricing policy whereas ezetimibe has taken only one price reduction in April 2016 of 5%. The PBAC noted that the ezetimibe component was the largest contribution to the price of statin plus ezetimibe combinations.  The PBAC asked the Minister to consider a review of the cost-effectiveness of ezetimibe. The PBAC noted that any such review should take into account the latest available evidence and best practice.

In July 2014, the PBAC reiterated this view in considering the ezetimibe plus rosuvastatin fixed dose combination (FDC).

In October 2014, the DUSC undertook an analysis of PBS utilisation of subsidised ezetimibe with simvastatin products. The analysis found that:

* The number of new patients commencing ezetimibe in any presentation was steady, with approximately 38,000 new patients each year. The number of prevalent patients on ezetimibe was increasing over time, and the majority of patient use was ezetimibe added to a statin.
* The listings of the 10-10 mg and 10-20 mg FDCs of ezetimibe plus simvastatin were expected to replace the concomitant use of ezetimibe and simvastatin. This was not the case and twelve months after listing use of these two formulations had increased:
	+ The number of patients taking ezetimibe + simvastatin 10 mg or 20 mg (as the concomitant agents or in a FDC) increased from 9,800 to 12,872.
	+ An additional 3,096 people were on the 10-10 mg and 10-20 mg FDC forms, but only 24 fewer patients were on the concomitant agents. That is, the FDC did not substitute for the concomitant agents as expected.
* Analysis of the streamlined authority code data indicated that the majority of ezetimibe use as an ‘add on’ to a statin was in patients inadequately controlled on the maximum tolerated dose of a statin.

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.

### B.3.2 PBAC recommendation

In August 2015, the PBAC considered the history of PBAC recommendations to list ezetimibe (as a single preparation or in combination with a statin), the DUSC utilisation reports for ezetimibe, PBS utilisation and financial cost data, and pricing relativity information for all PBS-listed lipid modifying agents and recommended that a PMR be undertaken.

On 28 September 2015, the Minister approved the commencement of the PMR of Ezetimibe, including the draft TOR. The commencement of the Review was announced on 16 October 2015, and submissions were sought on the draft TOR.

The PBAC subsequently reviewed stakeholder submissions and finalised the TOR on 11 December 2015, and the Minister approved the final TOR on 24 February 2016.

Medicines included in the PMR of Ezetimibe were:

* ezetimibe
* ezetimibe and atorvastatin
* ezetimibe and simvastatin
* ezetimibe and rosuvastatin.

An overview of the Repatriation PBS (RPBS)/PBS use and cost for ezetimibe and ezetimibe combination products for the twelve months from 1 July 2015 to 30 June 2016 is provided in Table 2.

Table 2: RPBS/PBS utilisation of ezetimibe and combination products July 2015-June 2016

|  |  |  |  |
| --- | --- | --- | --- |
| **Medicine** | **Prescriptions dispensed** | **Benefits** | **Patients** |
| Ezetimibe | 1,190,359 | $66,752,970.67 | 446,748 |
| Ezetimibe + Atorvastatin | 191,819 | $11,025,824.62 | 80,832 |
| Ezetimibe + Simvastatin | 985,546 | $58,206,343.03 | 364,862 |
| Ezetimibe  +  Rosuvastatin | 199,470 | $11,471,063.27 | 81,737 |
| **Total**Source: Department of Human Services website accessed 23 November 2016, based on date of supply data  | **2,567,194** | **$147,456,202** | **974,179** |

### B.3.3 Undertaking the Review

***B.3.3.1 Analysis and evaluation of scientific literature, utilisation data and additional relevant information***

The Department of Health (Health) commissioned Deakin University (Deakin) to undertake the following analyses and evaluations of the evidence to meet the Review TOR:

* Identification and summary of clinical evidence for ezetimibe (administered as monotherapy or combination therapy) in the treatment of hypercholesterolaemia not previously considered by the PBAC.
* Identification of published health economic models for ezetimibe and consideration of the applicability of the model structure and inputs to the Australian health system.
* A review of the current utilisation of ezetimibe in Australia, as monotherapy and in combination therapy.
* A review of recent clinical guidelines for the treatment of hypercholesterolaemia.

The executive summaries of each evaluation report for the TOR are provided in Sections 2, 3 and 4. A complete copy of the report is available from the Review Secretariat and published on the [Review website](http://www.pbs.gov.au/info/reviews/post-market-review-ezetimibe).

#### B.3.3.2 Stakeholder consultation

There were four formal opportunities for public stakeholder consultation on the PMR of Ezetimibe:

* on the draft TOR
* on the Review
* through a stakeholder forum
* on the draft Review report.

## B.4 Epidemiology of hypercholesterolemia

Large numbers of Australians have high cholesterol concentrations. High cholesterol is a major risk factor for coronary heart disease, stroke, peripheral vascular disease, and premature death.

In 2003, around 6% of the burden of disease and injury in Australia was attributed to high cholesterol, making it fifth out of fourteen risk factors examined. High blood cholesterol was the second most important contributor to the cardiovascular disease burden (after high blood pressure)[[18]](#endnote-19).

In 2013, ischaemic heart disease was the leading cause of death in Australia, accounting for around 20,000 deaths; cerebrovascular disease (including stroke) was the third leading cause of death. However, the number of deaths for which heart and cerebrovascular disease were an underlying cause has declined since 2004.[[19]](#endnote-20) Cardiovascular disease was also the second leading cause of fatal burden of disease (years of life lost) in Australia in 2010, accounting for 23% of the fatal burden of disease[[20]](#endnote-21).

The 2011-12 Australian Health Survey showed that 32.8% of Australian adults, or 5.6 million people, had abnormal concentrations of total cholesterol (>5.5 mmol/L), yet only around one in ten of these people self-reported high cholesterol as a current health condition. In addition, 76.4% of adults aged 45 years and over had dyslipidaemia, i.e. they were taking lipid lowering medication, or had one or more of the following: high total cholesterol, low HDL cholesterol, high LDL cholesterol, or high triglyceride.

### B.4.1 What are cardiovascular disease risk factors[[21]](#endnote-22)?

Cardiovascular disease includes coronary heart disease (myocardial infarct and angina), stroke, and other vascular disease such as peripheral arterial disease and renovascular disease. When a patient has one of these diseases this is referred to as a cardiovascular event.

Longitudinal epidemiological studies have shown that the majority of patients who develop a cardiovascular event have identifiable and modifiable cardiovascular risk factors that are amenable to behavioural and therapeutic (including drug) interventions. Improvements in the management of major risk factors such as smoking, elevated blood pressure (BP) and dyslipidaemia have led to a marked decline in the overall death rate for cardiovascular disease in the past 20 years.

People with any of the following risk factors are already known to be at high risk of a cardiovascular event

* established cardiovascular disease
* diabetes and age more than 60 years
* diabetes with microalbuminuria (more than 20 µg/min, or urinary albumin: creatinine ratio more than 2.5 mg/mmol for men or more than 3.5 mg/mmol for women)
* moderate or severe chronic kidney disease (persistent proteinuria or estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m2)
* a previous diagnosis of familial hypercholesterolaemia
* systolic BP 180 mm Hg or more, or diastolic BP 110 mm Hg or more
* serum total cholesterol more than 7.5 mmol/L
* Aboriginal and Torres Strait Islander adults aged more than 74 years

Where people have one or more risk factors for developing cardiovascular disease the treatment of dyslipidaemia is usually commenced at lower blood concentrations of LDL or total cholesterol. For the purpose of subsidised treatment on the PBS, the qualifying criteria for commencing treatment with a lipid lowering medicine is set out in the ‘General Statement for Lipid Lowering Drugs Prescribed as Pharmaceutical Benefits’.

For patients at moderate absolute CVD risk (10% to 15%), lipid-modifying therapy may be warranted (after 3 to 6 months of dietary and behavioural risk factor modification) if there is a family history of premature CVD (i.e. first-degree relative who developed CVD before age 60 years).

### B.4.2 What is dyslipidaemia?

Dyslipidaemia[[22]](#endnote-23) is the elevation of plasma cholesterol, triglycerides, or both, or a low HDL cholesterol concentration that contributes to the development of atherosclerosis. Causes may be primary (genetic) or secondary. Diagnosis is by measuring plasma concentrations of total cholesterol, triglycerides, and individual lipoproteins. The best approach to therapy for a particular patient depends on the nature of the predominant dyslipidaemia. Before starting drug therapy, it is necessary to confirm that the dyslipidaemia is not secondary to a treatable problem. Treatment of dyslipidaemia is generally life-long.

### B.4.3 What is familial hypercholesterolaemia?

Familial hypercholesterolaemia[[23]](#endnote-24) is a dominantly inherited condition that affects over 1 in 500 people and leads to the onset of CVD 20 to 40 years earlier than in someone without the condition. Approximately 50% of members in affected family groups are affected.

### B.4.4 Use of algorithms to estimate absolute risk of cardiovascular disease?

The PBS does not use a discrete absolute risk model as the basis for the qualifying criteria to commence treatment with LLT, but the GSLLD uses a risk-based approach.

Absolute risk models have been developed and validated in a number of countries. In Australia, the National Vascular Disease Prevention Alliance (NVDPA) absolute CVD risk calculator and charts provide publicly accessible tools to estimate risk[[24]](#endnote-25).

Absolute CVD risk is defined as the probability (expressed as a percentage) of a person having a cardiovascular event within a specified period of time. The NVDPA risk calculators categorise a person's risk over 5 years: high absolute risk (more than 15%), moderate absolute risk (10% to 15%), or low absolute risk (less than 10%).

### B.4.5 Treatment guidelines

A number of clinical guidelines for the treatment of dyslipidaemia are published in Australia and internationally. Section three of this report provides a review of the current clinical guidelines for the treatment of hypercholesterolaemia in accordance with TOR 2.

# Section 1: TOR 1Utilisation of ezetimibe

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.

## 1.1 Key findings for TOR 1

The analysis of PBS data addressed the following research question:

***“Is ezetimibe being prescribed on the PBS in accordance with the restrictions for ezetimibe which require patients to be treated with a maximally tolerated dose of statin before initiation of treatment with ezetimibe?”***

The following results are summarised from the full report **(December 2016 and March 2017 Analyses)** of PBS ezetimibe utilisation prepared by the Centre for Population Health Research (CPHR), Deakin University, provided at **Appendix E.**

* The number of people initiating ezetimibe in 2014-15 was 45,465.
* Analysis of all ezetimibe initiators in the 12 month period from 1 April 2014 to 31 March 2015 (2014-2015) found that 6,938 (or 15%) had no prior lipid lowering therapy dispensed in the prior 24 months (Cohort 1) and 38,707 (or 85%) had at least one lipid lowering prescription dispensed (Cohort 2) in the prior 24 months. The majority (97.7%) of Cohort 2 had received at least one statin prescription.
* A significant number 16,344 (42.3%) of Cohort 2 had filled less than three statin prescriptions in the 6 months prior to ezetimibe initiation. While this study did not measure adherence specifically, there appears to be poor adherence to statin therapy prior to initiating ezetimibe in this group.
* A large number 26,676 (69%) of Cohort 2 patients remained on the same statin (in terms of the potency or dose) throughout the 24 months pre-ezetimibe period. It is not possible to know from PBS data if these people have been optimally treated with a statin, however approximately 20% (5,344) were receiving the highest dose of a high intensity statin.
* In the **December 2016 Analysis** the following groups were considered to have not complied with the PBS restriction for ezetimibe:
* people in Cohort 1 who initiated ezetimibe in combination with a statin or later added statin
* people in Cohort 2 who up-titrated their statin dose or potency following initiation of ezetimibe.

On this basis the **December 2016 Analysis** estimated that 15.9% of new users of ezetimibe had not complied with the PBS restriction.

* Following DUSC consideration of the December 2016 Analysis, a second analysis was conducted by CPHR, Deakin, provided at **Appendix E (Section 2.4 p. 8).** The **March 2017 Analysis** was conducted in the same PBS dataset and the same Cohorts (1 and 2) as identified in the December 2016 Analysis. In addition, the March 2017 Analysis categorised all new users of ezetimibe according to both pre and post use of statins and other LLT into the following three groups:

• those initiating ezetimibe in accordance with the PBS restriction (green);

• those initiating ezetimibe in a manner that is not consistent with the PBS restriction (red);

• the remainder for whom compliance with the PBS restriction is unknown (orange).

* **The March 2017 Analysis** found that 46.9 % of patients were in the ‘green’ group described above, 18.4% of patients were in the ‘red’ group and 34.8% of patients were in the ‘orange’ group.
* The Reference Group noted stakeholder input that acknowledged the prescribing of ezetimibe ahead of up-titration of statins to avoid adverse effects.

## 1.2 Summary of Ezetimibe Utilisation Analysis

### 1.2.1 Methods – December 2016 analysis

Pharmacy claim data for all PBS prescriptions were used to analyse utilisation of ezetimibe in Australia. All PBS medicines coded Anatomical Therapeutic Classification (ATC) C10 dispensed from 1 April 2012 to 31 July 2016 were extracted from the PBS dataset (111.5 million records). The PBS dataset for this period contains records for all PBS prescriptions including those priced under the patient co-payment; it does not include private prescriptions or samples provided by industry. All records were sorted by date of supply.

From this dataset the eligible study population was identified as people who received their first dispensing supply of ezetimibe between 1 April 2014 and 31 March 2015. Initiation to ezetimibe (index date) was determined on the basis that there was no previous dispensing of ezetimibe for a minimum of 24 months look back.

The total eligible population of initiators to ezetimibe was then divided into two cohorts for analysis:

* **Cohort 1** – people who did not receive any dispensing for a C10 medicine (statin or other LLT) in the 24 months prior to initiation of ezetimibe.
* **Cohort 2** – people who received one or more prescriptions of a C10 medicine in the 24 months prior to initiating ezetimibe.

**Cohort 1 Analysis** - included follow-up of all lipid lowering medicines dispensed in the 12 months post the ezetimibe index date.

**Cohort 2 Analysis** – prior use of statins was analysed according to: the number of statins dispensed in the prior 24 months; the number of people continuously using statins (three or more prescriptions) in the six months prior to ezetimibe initiation; and the number of people with a switch between statins or adjustment of statin dose.

Following the ezetimibe index date, use of any C10 medicines was followed for 12 months for all individuals in Cohort 2.

### 1.2.2 Results - December 2016 analysis

A total of 45,645 patients were initiated on ezetimibe in the 12 months from April 2014 to March 2015. Just over 15% (n=6,938) of these patients had no prior dispensing for any lipid lowering medicines in the previous 24 months (**Cohort 1**); 85% (n=38,707) had received at least one prescription for a C10 medicine (**Cohort 2**).

A summary of the population first prescribed ezetimibe between 1 April 2014 and 1 April 2015 is shown in the following table:

Table 3: Summary of the population first prescribed ezetimibe in the base year

|  |  |  |  |
| --- | --- | --- | --- |
| **Cohort No.** | **No. of patients**  | **Mean number (SD) of statin prescriptions dispensed in 24 months prior to ezetimibe initiation** | **Mean number (SD) of non-statin prescriptions dispensed in 24 months prior to ezetimibe initiation** |
| Cohort 1 | 6,938 (15%) | 0 | 0 |
| Cohort 2 | 38,707 (85%) | Mean: 13.49±8.425Median (IQR): 14 (6-21)  | Mean: 0.98±3.966Median (IQR): 0 (0-0)  |
| **Total**  | 45,645 (100%) | - | - |

SD=standard deviation; IQR=interquartile range, Cohort 1: no prior dispensing for any lipid lowering medicines in the previous 24 months, Cohort 2: received at least one prescription for a C10 medicine in the previous 24 months

Source: Ezetimibe Review Analysis of Utilisation Data, CPHR Table 4.1, p13

1.2.2.1 Statin utilisation prior to ezetimibe (Cohort 2)

In order to examine the question of whether or not patients were being treated optimally with statin therapy, the pattern of supply of statin prescriptions in the six months prior to initiation of ezetimibe for each patient was examined in detail. The results are presented in Table 4 below. Continuous treatment was defined as 3 or more supplies in the six months prior to index ezetimibe. This is a conservative assumption to allow for patients who may have some additional prescription supplies on hand due to stockpiling that typically occurs around the end of the calendar year.

Table 4: Distribution of Cohort 2 patients across the number of dispensed statin prescriptions

|  |  |
| --- | --- |
| Number of statin prescriptions dispensed in 6 months prior to ezetimibe initiation | Number/Proportion of patients |
| ***New to statin therapy i.e. no statin dispensed in the period 6 to 24 months prior to ezetimibe initiation*** |
| One-two statin prescriptions dispensed | **1,883 (4.9%)** |
| ***Commenced statin therapy more than 6 months prior, and ≥ 3 statin script dispensed (continuous treatment) in the 6 months prior to ezetimibe initiation*** |
| Three statin prescriptions dispensed | 3,707 (9.6%) |
| Four statin prescriptions dispensed | 4,010 (10.3%) |
| Five statin prescriptions dispensed  | 6,275 (16.2%) |
| Six statin prescriptions dispensed | 6,537 (16.9%) |
| >six statin prescriptions dispensed | 1,834 (4.7%) |
| **Sub-total** | **24,246 (57.7%)** |
| Less than three prescriptions dispensed\* | 14,461 (37.4%) |
| **Total** | **38,707 (100%)** |

*\*Have also had statin dispensed in period 6 -24 months prior to index ezetimibe*

Cohort 2: received at least one prescription for a C10 medicine in the previous 24 months

Source: Ezetimibe Review Analysis of Utilisation Data, CPHR Table 4.1.1, p 15

In Cohort 2, 57.7% of patients were considered to have received continuous treatment with a statin (i.e. at least 3 dispensings in the previous 6 months prior to index ezetimibe). A further 4.9% were considered to have initiated statin treatment in the 6 months prior to initiation of ezetimibe and 37.4% were considered not to be on continuous statin therapy in the 6 months prior to the index ezetimibe date.

There are a number of possible reasons for patients commencing ezetimibe with a history of non-continuous statin use. Some of these patients may have had adverse events and not returned immediately to their general practitioner to seek further treatment for dyslipidaemia, or were reluctant to continue treatment with a statin. Other patients may represent those who are non-adherent to statin therapy i.e. do not take their medication consistently.

The supplies of types and strengths of statins dispensed prior to ezetimibe were examined for patients in Cohort 2. The study assumed that patients seeking to optimise LLT, consistent with guideline recommendations and PBS restrictions, would be titrating statin therapy or be taking higher strengths of the more potent statins.

For patients in Cohort 2, the analysis found that 68.9% (26,676/38,707) remained on the same statin dose or potency in the 2 years preceding ezetimibe initiation (Table 5). However approximately 50% were dispensed high intensity statins (Table 6 below)

Another 11,124 patients in Cohort 2 had evidence of either up, down or both up and down titration of statins (Table 5). Therefore, at least 34.8% of Cohort 2 would appear to meet the PBS restriction requirement that patients are treated with the maximum tolerated dose of a statin prior to initiating ezetimibe.

Table 5: Proportion of the total Cohort 2 patients in each of the categories of the 24-month pre-ezetimibe history of LLT

|  |  |
| --- | --- |
| 24-month pre-ezetimibe LLT | **No. of patients** **(Total N=38,707)** |
| Remained on non-statin LLT\* | 907 (2.3%) |
| Remained on the same statin dose or potencyǂ | 26,676 (68.9%) |
| Up-titration only of statin dose or potency | 4,525 (11.7%) |
| Down-titration only of statin dose or potency | 2707 (7.0%) |
| Both up- and down- titration of statin dose or potency | 3,892 (10.1%) |

**\***the dose change in non-statin LLT was not examined

**ǂ “**remained on the same dose” means that a patient had at least two statin prescriptions dispensed during the pre-ezetimibe period and did not experienced any up- or down-titration either in terms of a dose or a potency of a statin.

Source: Ezetimibe Review Analysis of Utilisation Data, CPHR Table 4.1.2, p16

Table 6: Cohort 2: Remained on the same dose or potency of statin prior to ezetimibe initiation (N=26,676)

|  |  |
| --- | --- |
| **Potency of statin** | **No. of patients (%)** |
| *Low-intensity statin* | 649 (2.4%) |
| Moderate-intensity statin | Lower dose | 4,301 (16.1%) |
| Higher dose | 8,202 (30.7%) |
| *Moderate intensity statin (subtotal)*  | 12,503 (46.9%) |
| High-intensity statin | Lower dose | 8,180 (30.7%) |
| Higher dose | 5,344 (20.0%) |
| *High intensity statin (subtotal*) | 13,524 (50.7%) |

Source: Ezetimibe Review Analysis of Utilisation Data, CPHR Table 4.1.3, p 16

1.2.2.2 Lipid lowering therapy post ezetimibe initiation

The December 2016 Analysis provided a limited analysis of changes in LLT for patients in the 12 months post initiation of ezetimibe for both Cohort 1 and Cohort 2 (see **Appendix E** p.21 Table 4.2.5). This analysis was respecified in the March 2017 Analysis and is therefore not presented here to avoid confusion.

1.2.2.3 Estimate of PBS population not meeting PBS restriction – December 2016 analysis

In the December 2016 the following groups were considered to have not complied with the PBS restriction for ezetimibe: people in Cohort 1 who initiated ezetimibe in combination with a statin or later added statin; and those in Cohort 2 who up-titrated their statin dose or potency following initiation of ezetimibe. On this basis the December 2016 Analysis estimated that 15.9% of new users of ezetimibe had not complied with the PBS restriction.

### 1.2.3 Background - March 2017 analysis

The DUSC reviewed the results of the initial December 2016 Analysis in February 2017 and requested an additional analysis using the same dataset be conducted to more comprehensively answer the above research question to address TOR 1. The DUSC’s view was that not all utilisation pre and post ezetimibe initiation had been linked at the individual patient level and that this was likely to have underestimated the number of patients who were not using ezetimibe in accordance with the restriction.

DUSC was also concerned that some of the methodology for the analysis of PBS data was not sufficiently defined in the report and suggested further clarification of these methods should be provided along with any additional analysis of the data.

### 1.2.4 Methods - March 2017 analysis

The approach for the additional analysis of PBS prescription data replicates and expands on the approach described in the original report (see **Appendix E** Section 2.3 p.8). Pre- and post-ezetimibe history of statin use was linked by identifying patients in Cohort 2 in whom statin therapy was up-titrated at the time of, or after, initiation of ezetimibe. This approach allows for an estimation of the use of ezetimibe on the PBS, which is inconsistent with the PBS restriction.

DUSC suggested that the following three groups could be more accurately identified in PBS data:

• those initiating ezetimibe in accordance with the PBS restriction (green);

• those initiating ezetimibe in a manner that is not consistent with the PBS restriction (red); and

• the remainder for whom compliance with the PBS restriction is unknown (orange).

The tables representing the decision matrix for classifying patients into these three groups (red, green and orange) according to the history of dispensing of lipid lowering medicines before and after initiating ezetimibe are presented in **Appendix E**, March 2017 Analysis, Tables B1 and B2, p 36. These tables were presented to the Reference Group on 17 March 2017, to seek additional clinical input and agreement on the colour coding of each cell in the decision matrix. All coloured cells include discrete patient numbers from Cohort 1 and Cohort 2.

This additional analysis used the same study population identified in Deakin’s ezetimibe utilisation December 2016 Analysis (**Appendix E,** p 2) i.e., people who received their first prescription for ezetimibe between 1 April 2014 and 31 March 2015. Initiators to ezetimibe were further categorised into the following two cohorts, those with:

* no history of statin or non-statin LLT in the 24 months prior to ezetimibe initiation (**Cohort 1**)
* a history of statin or non-statin LLT in the 24 months prior to ezetimibe initiation (**Cohort 2**).

Additional analyses of sub-groups of those in Cohort 2 were also conducted (see below).

Compliance with ezetimibe restrictions requires consideration of the nature of both pre and post ezetimibe LLT utilisation. Titration of statin dose/potency was considered pre ezetimibe initiation. Post ezetimibe statin dose was then compared with patient’s pre statin doses to ascertain if up-titration had occurred following initiation of ezetimibe. This pattern of dispensing would indicate that these patients had not been optimally titrated with statins prior to commencing ezetimibe.

#### Definitions

*Initiation to ezetimibe*: individuals dispensed their first prescription for ezetimibe or a FDC containing ezetimibe between 1 April 2014 and 31 March 2015 in the dataset.

*Initiation to combination ezetimibe and statin (or other LLT)*: individuals dispensed a statin or other LLT on the same day or within the following 30 days of the ezetimibe initiation date.

Among patients in Cohort 2, prior use of LLT was categorised into eight groups, defined in Table 7 below.

Table 7: Definitions of lipid lowering use prior to ezetimibe initiation (applicable to Cohort 2)

|  |  |
| --- | --- |
| Ceasing statin therapy | Received statin in the 24 months prior, but did not have any statin prescriptions dispensed in the 6 months immediately prior to initiating ezetimibe |
| Patients with at least one statin prescription dispensed in the 6 months prior to ezetimibe initiation |
| Mutually exclusive groups  | Down-titrated statin only or on the lowest statin dose |
| Up-titrated statin only, but not to the highest statin dose |
| Last dose of statin before ezetimibe initiation was the highest dose of statin (including those who were up-titrated to the highest dose) |
| Stayed on the same dose of statin which was neither the highest nor the lowest dose of statin |
| Both up- and down- titrated statin (excluding those who were on the highest dose and lowest dose prior to initiation) |
| Patients with prior non-statin LLT only | Over the 24 months prior to ezetimibe initiation, no statin prescriptions were dispensed, but at least one non-statin LLT prescription was dispensed  |

The additional analysis of the 12 months post ezetimibe LLT use was primarily focused on patients described in Table 8. However, no analysis of the full 12 months post ezetimibe was conducted on those in Cohort 1 who were initiated on ezetimibe plus statin (all considered to be use outside of the restriction) or ezetimibe plus non-statin LLT (all considered to be use within the restriction). Although there is a possibility that among those who initiated therapy with ezetimibe plus non-statin LLT may have added a statin over the following 12 months (which would represent use of ezetimibe outside of the restriction), this population of 40 patients represents less than 0.1% of the entire study population (N=45,645) and their exclusion from this further analysis had minimal effect.

Table 8: Definitions of LLT use after ezetimibe initiation for both Cohort 1 and 2

| **Cohort**  | **Status at initiation and follow – up of 365 days** |
| --- | --- |
| Cohort 1  | Initiate and remain on ezetimibe monotherapy  |
| Initiate ezetimibe in combination with a statin or later add or switch to therapy involving a statin  |
| Initiate ezetimibe in combination with or later add/switch to a non-statin LLT |
| Cohort 2  | Initiate and remain on ezetimibe monotherapy (i.e., receive no other LLT)  |
| Initiate ezetimibe in combination with statin at higher intensity\* or later add/ switch to statin at higher intensity\* |
| Initiate ezetimibe in combination with statin at same intensity\*\* or later add/ switch to statin at same intensity\*\* |
| Initiate ezetimibe in combination with statin at lower intensity\*\*\* or later add/ switch to statin at lower intensity\*\*\* |
| Initiate and remain on ezetimibe in combination with other non-statin LLT or, add/switch to other LLT  |

\* If any statin prescriptions post ezetimibe initiation (365 days) at higher intensity than last statin strength dispensed before starting ezetimibe

\*\* Patients with the highest intensity in all statins prescribed in post-ezetimibe period being equal in intensity to the last pre-ezetimibe statin

\*\*\* If all statin prescriptions post ezetimibe initiation at a lower intensity than the last statin pre-ezetimibe statin prescription

References to the highest and lowest statin doses and changes resulting from up or down titration of statins described in Table 8 are defined in Figure 1.

**Figure 1: Definitions applied in this analysis for “highest” and “lowest” dose statins and movement from higher to lower (or lower to higher) intensities and doses assumed to be the “same” across statins**

**Down-titration to lower intensity**

|  |  |  |
| --- | --- | --- |
| **High potency statin** | **Moderate potency statin** | **Low potency statin** |
| **Highest dose** Atorvastatin, 80mgRosuvastatin, 40 mg | Atorvastatin, 40 mgRosuvastatin, 20 mgSimvastatin 80 mg | Atorvastatin, 20 mgRosuvastatin, 10 mgSimvastatin, 40 mgPravastatin, 80mgFluvastatin, 80mg | Atorvastatin, 10 mgRosuvastatin, 5 mgSimvastatin, 20 mgPravastatin, 40mg | **Lowest dose\***Simvastatin, 5-10 mgPravastatin, 10-20mg |

**Up-titration to higher intensity**

\* As defined in Table 5 of Stone et al 2013[[25]](#endnote-26), the “lowest” dose aggregates two strengths of simvastatin (5mg and 10 mg) and two strengths of pravastatin (10 and 20mg)

***1.2.5 March 2017 analysis - Results***

Of the 45,645 patients who were first dispensed ezetimibe between 1 April 2014 and 31 March 2015, 6,938 patients were represented in Cohort 1 (had no history of LLT in the 24 months prior to ezetimibe initiation) and 38,707 patients were represented in Cohort 2 (had a history of LLT in the 24 months prior to ezetimibe initiation).

In Cohort 1, 3,148 patients initiated on ezetimibe monotherapy and stayed on monotherapy for the next 12 months. This number includes patients with a single ezetimibe prescription. There is insufficient evidence to establish compliance with the PBS restriction in this subgroup of Cohort 1 patients and they are therefore considered part of the orange group. A further 3,647 patients initiated ezetimibe and received a statin in the following 12 months (red group). The remaining 143 patients in Cohort 1 initiated ezetimibe and received only dispensings for other non-statin LLT in the following 12 months (green group). Results for Cohort 1 are summarised in Table 9.

Table 9: Results Cohort 1 (patients initiating ezetimibe with no prior dispensing of any LLT in the 24 months prior to ezetimibe initiation; N=6,938)

| **LLT in prior 24 months** | **Post-ezetimibe LLT (followed for 12 months)** |
| --- | --- |
| stay on ezetimibe monotherapy | start/add/switch to a statin | switch or add non-statin LLT |
| No LLT | N=3,148 (45.4%) | N=3,647 (52.6%) | N=143 (2.0%) |

In Cohort 2, a total of 4,713 patients were found to have patterns of statin dispensing that suggested further up-titration occurred following initiation to ezetimibe and were grouped red. A further 21,243 patient’s LLT dispensing patterns suggest that they were initiated to ezetimibe in accordance with the PBS restriction and were grouped as green. It was unclear from the dispensing patterns of the remaining 12,751 patients, whether or not they were treated in accordance with the PBS restrictions and were grouped orange. Results for Cohort 2 are summarised in Table 10.

**Table 10: Cohort 2 according to use of LLT pre and post ezetimibe initiation N=38,707**

| **Pre Ezetimibe LLT** | **No.** | **Post-ezetimibe LLT (followed for 12 months)** |
| --- | --- | --- |
| stay on ezetimibe monotherapya | start/add/switch statin to higher dose\*,b | start/add/switch statin to same dose\*\*,b | start/add/switch statin to lower dose\*\*\*,b | start/stay/add other LLT onlyc |
| Ceased statin more than 6 months prior ezetimibe | 7,327 | 3,327 | 615 | 1,545 | 1,587 | 253 |
| Down titrated statin or on lowest dose | 2,837 | 912 | 601 | 1,022 | 222 | 80 |
| Up titrated statin ( not on highest) | 2,401 | 306 | 258 | 1,285 | 515 | 37 |
| On highest dose of statin | 6,986 | 245 | N/A | 4,930 | 1,778 | 33 |
| Stayed on same dose of statin | 15,616 | 3,147 | 1,787 | 8,022 | 2,463 | 197 |
| Up and down titrated statin | 2,633 | 331 | 517 | 1,320 | 425 | 40 |
| All other LLT (no statin) | 907 | 303 | 384 | 220 |

N/A= not applicable, LLT = lipid lowering therapy

Grey cells pre ezetimibe indicate that at least one statin prescription was dispensed in the 6 months prior to starting ezetimibe

\* If any statin scripts post ezetimibe initiation (365 days) at higher dose than last statin strength dispensed before starting ezetimibe

\*\* Patients with the highest intensity in all statins prescribed in post-ezetimibe period being equal in intensity to the last pre-ezetimibe statin

\*\*\* If all statin scripts post ezetimibe initiation at a lower dose than the last statin pre-ezetimibe statin script

a only relevant to those initiating ezetimibe monotherapy

b applies to all initiators (ezetimibe monotherapy, ezetimibe + statin combination or ezetimibe + non-statin LLT) combination.

 For those initiating on ezetimibe + statin combination, this may represent the single initiating statin intensity

c only relevant to those initiating ezetimibe monotherapy and ezetimibe + non-statin LLT combination therapy

Of the 45,645 patients included in the March 2017 Analysis (Cohorts 1 and 2):

* 143 + 21,243 = 21,386 (46.9%) filled LLT prescriptions in a manner that *was in accordance with the PBS restriction* for ezetimibe;
* 3,647 + 4,713 = 8,360 (18.4%) filled LLT prescriptions in a manner that was *not in accordance with the PBS restriction* for ezetimibe; and
* 3,148+ 12,751 = 15,899 (34.8%) filled LLT prescriptions in a manner in *which accordance with the PBS restriction for ezetimibe is unknown.*

## 1.3 Key issues raised by stakeholders on TOR 1

Details of the submissions to the Review and responses to the Stakeholder Forum Outcome Statement are provided in **Appendix F** and **Appendix H**, respectively.

### 1.3.1 Submissions to the Review

In the seven week public consultation held between 4 March and 22 April 2016 stakeholders raised the following key points in relation to TOR 1:

* Prescribers in the community setting write the majority of prescriptions.
* Access to non-statin therapies is important for patients who are unable to achieve treatment targets, or for those who are unable to tolerate statins.
* Ezetimibe is the predominant non-statin therapy reflecting the focus on LDL‑C as the primary treatment target.
* The submission from the sponsor of ezetimibe included an analysis of PBS data (10% sample) between 2010 and 2015. The sponsor claims that 88.5% of all PBS use of ezetimibe is in accordance with the PBS restriction. This analysis was limited to concessional patients and is potentially misleading as individual patients had the potential to initiate ezetimibe and ezetimibe/statin FDC on multiple occasions.

### 1.3.2 Outcomes from the stakeholder forum

Participants made a number of comments relevant to the evidence collated under TOR 1 and the questions posed by the Reference Group.

In relation to the study finding that 68.9% of Cohort 2 patients had not had their statin dose increased, it was suggested that clinicians may be choosing to not titrate to the maximum tolerated dose to avoid side-effects such as muscle aches and pains.

In considering sources of evidence available to assist in determining the size of the population truly contraindicated to statins, participants acknowledged that there were studies available and agreed to provide information to the Review Secretariat. Following the stakeholder forum the sponsor provided the citations.

The difference between intolerance and contraindication was discussed. Participants suggested that although patients say they are intolerant to statin therapy, only a small proportion of patients are truly intolerant to statins. For example, clinical trials show that approximately 1-5% of patients are intolerant, with possibly up to 10% of patients partially intolerant.

Participants also commented that negative publicity from the Catalyst program (ABC, October 2013) has had a significant impact on patient perceptions and preferences and may impact on the proportion of patients that start ezetimibe without having first taken a statin.

It was also suggested that in considering the rationale for initiating ezetimibe without first trialling a statin alone, the figure of 15% (Cohort 1 patients who 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 non-concessional 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 plus ezetimibe combination without a statin trial may occur in the clinical situation where LDL-C is high and needs reducing quickly.

The [Stakeholder Forum Outcome Statement](http://www.pbs.gov.au/reviews/ezetimibe-review-files/ezetimibe-stakeholder-forum-outcomes-report.pdf) is available on the Review website. Stakeholder responses to the Stakeholder Forum Outcome Statement are available on the Review’s [Public Consultation website](http://www.pbs.gov.au/info/reviews/ezetimibe-review-public-consultation).

### 1.3.3 Stakeholder submissions to the draft Report

Stakeholders raised the following points in their responses to the draft Report provided on the PMR website for public consultation from 30 January to 10 February 2017.

* That a small proportion of people were likely to be non-adherent to the PBS restrictions, but no submissions considered this was a significant problem.
* Statin intolerance occurs in about 10% of patients but 20% of patients report side-effects, especially muscle aching.
* The reasons put forward in the report for patients commencing ezetimibe without trialling maximal doses of statins were clinically reasonable.
* Submissions were supportive of measures to improve prescriber, pharmacist and patient education and to promote programs that support patients being compliant to therapy.
* Prescribers and patients place significant value on ezetimibe’s ability to lower LDL-C and event risk without increasing the likelihood of adverse effects associated with higher statin doses (MSD January 2017 response, p 2).

This last point further reinforced the Reference Group’s view that there is a significant patient population for whom ezetimibe is added to statin therapy before maximum tolerated doses of statins are trialled.

## 1.4 Reference Group consideration

The Reference Group has considered the evidence provided in the evaluators’ report on current utilisation of PBS-listed ezetimibe and ezetimibe combination products, stakeholder input and its collective views for this TOR.

### 1.4.1 Compliance with PBS restrictions

From the December 2016 Analysis, 15% of patients had no prior exposure to statins or other LLT in the 24 months prior to the first use of ezetimibe. Analysis of all ezetimibe initiators in 2015-16 found that 6,408 (or 12%) had no prior lipid lowering therapy dispensed in the prior 36 months. This would indicate that a longer look back period is likely to detect further LLT history. The Reference Group noted stakeholder views that there are a number of reasons why the Cohort 1 patients initiate ezetimibe or ezetimibe statin combination therapy without prior statin use. It was also noted that the number of patients intolerant or contraindicated to statins was likely to be much lower than the 15% reported in the utilisation study, but that the final number was difficult to estimate from these data alone.

The December 2016 Analysis also reported that 30% of patients with a prior history of statin or other LLT use (Cohort 2) have evidence of dose adjustment/manipulation, either up-titration or down-titration. This may reflect titration to increase response to the medicine, or be in response to the patient experiencing adverse effects. For the significant proportion of patients (70%) who remain on the same dose of statin, the data is insufficiently detailed to demonstrate that they were or were not already on the maximum tolerated dose of statin. However, 50% of the patients remaining on the same dose appear to be using a high intensity statin.

From Cohort 1 (patients without history of statins or other LLT in the prior two years), 53% of patients were initiated on ezetimibe monotherapy, and 45% initiated ezetimibe with a statin (40% as a FDC). These data are insufficiently detailed to show whether patients have had some statin exposure prior to the two year look back period, however, it may suggest that up to 45% of the Cohort 1 initiations of ezetimibe are in combination with a statin and would be considered outside the PBS restriction.

Whilst Cohort 2 patients initiated on ezetimibe plus statin combination therapy had a prior statin or LLT history, only 10% up-titrated their statin dose or switched to a statin of higher potency in the two year period. This indicates that statin use prior to the first prescription of ezetimibe was not at a maximally tolerated dose for many patients. This would also indicate use outside the PBS restriction.

Taking the results of the March 2017 Analysis into account, the Reference Group considered the estimate of ezetimibe use outside the PBS restriction would fall somewhere in the range of 18.4% - 53.2% i.e. the proportion of use categorised as red (outside restriction) and an unknown proportion of use categorised as orange (uncertain). The Reference Group acknowledges the wide range, but considers that this is the best estimate due to the limitations of the PBS data. Ezetimibe use that does not appear to comply with the PBS restriction may in some cases be clinically appropriate, however is unlikely to be cost-effective.

The Reference Group also suggested that for the 18.4% – 53.2 % of patients who use ezetimibe outside the PBS restriction, placebo is not the appropriate comparator for a cost-effectiveness analysis. The comparator for this group of patients should be a higher dose of statin or switching to a higher potency statin.

### 1.4.2 Adherence and persistence to LLT pre and post initiation of ezetimibe therapy

According to the December 2016 Analysis there appears to be an adherence and persistence issue with long-term LLT in the management of hyperlipidaemia in Australia. A significant proportion of patients prescribed ezetimibe had two or less statin prescriptions dispensed in the previous six months. Due to poor adherence, the effectiveness and cost-effectiveness of ezetimibe in clinical practice may differ from that demonstrated in clinical trials.

Following initiation to ezetimibe a significant proportion of patients did not continue to receive LLT therapy in the following 6-12 months. For Cohort 1, 44% and for Cohort 2, 11.6% of ezetimibe initiators ceased taking LLT between 6 and 12 months after initiating ezetimibe.

The Reference Group noted that a substantive proportion of patients may have ceased therapy for other reasons (including death). However, the Reference Group considered that these data show that persistence is particularly an issue when patients are commencing or recommencing LLT.

The Reference Group considered that this presented an educational opportunity for prescribers and consumers in reinforcing and promoting the message that for quality use of medicines and optimal management of LDL-C reduction, statins should be used first. Ezetimibe should only be prescribed after the statin dose has been optimised, unless the patient is contraindicated to statin therapy.

Recent literature also suggests that patients who take less than 80% of their statin dose have a 45% relative increase in total mortality compared with more adherent patients, an increase greater than that observed with poor adherence to other cardiac drugs. Cessation of statin treatment is associated with worse cardiovascular outcomes[[26]](#endnote-27),[[27]](#endnote-28).

While the December 2016 Analysis suggests poor adherence to therapy, the Reference Group acknowledges the DUSC advice that these studies were not designed specifically to examine questions of adherence or persistence. The analysis was limited to the population who were initiating ezetimibe and does not necessarily reflect adherence or persistence in the broader population taking statins. The DUSC agreed that new users of medicines are likely to be at higher risk of non-adherence.

# Section 2: TOR 2Clinical guidelines for the use of ezetimibe

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

## 2.1 Key findings for TOR 2

* The approach to treatment to prevent cardiovascular events is similar across the identified guidelines. The variation between Australian and international guidelines reflects differences in absolute risk thresholds and pharmacotherapy in each country.
* All guidelines consider diet and exercise should be the first step for patients with an elevated cardiovascular risk. Stakeholders noted the importance of these lifestyle changes to cardiovascular risk reduction.
* The majority of the guidelines list statins as the first pharmacotherapy of choice in patients who have increased risk of cardiovascular disease. Adding ezetimibe is usually recommended when patients require additional reduction of LDL-C. The rationale for this positioning of ezetimibe is not clearly articulated but is likely to reflect the greater body of evidence on clinical outcomes supporting statin use and the greater percentage reduction of LDL-C with statins compared to ezetimibe monotherapy.
* The majority of patients (82.7%) who commenced ezetimibe in the 2014/2015 period had a history of statin use in the 2 years prior to initiation. This would suggest that a substantial proportion of prescribers use statins as first line therapy in hyperlipidaemia.
* PBS restrictions may not reflect clinical guidelines. The PBS restrictions consider both comparative effectiveness and cost-effectiveness while guidelines can take greater account of individual patient efficacy and do not consider cost-effectiveness at the population level.
* Statins are well tolerated and the proportion of people who are truly contraindicated to statins is reported to be very small. There is some dispute about the exact size of the intolerant and contraindicated populations in Australia. Overall figures of 5-10% were considered reasonable by the Reference Group.
* Ezetimibe is one of the treatment options for patients in whom statin therapy is contraindicated or not tolerated. Strategies for managing statin intolerance include prescribing a different statin, taking a treatment break and rechallenging, or reducing the dose of statin.
* There are small differences between the eligibility of patients for pharmacotherapy between the GSLLD and the Australian guidelines for treatment. The effect of these differences has not been quantified, with one study indicating that it may not be substantial[[28]](#endnote-29).
* The Bohula et al[[29]](#endnote-30)  re-analysis of the IMPROVE-IT trial defined subgroups of participants according to the level of atherothrombotic risk. They found those who showed significant benefit from ezetimibe/statin therapy were in the highest cardiovascular risk category i.e. the secondary prevention group with three or more additional risk factors. This underlines the importance of restricting PBS subsidised use of ezetimibe to the high risk population.
* The use of LLT is now an established approach to reduce cardiovascular risk.

## 2.2 Published evidence

### 2.2.1 Approach to the literature review of clinical guidelines

A review of the most recent Australian and international clinical treatment guidelines for management of metabolic lipid disorders to prevent cardiovascular outcomes was undertaken. Eleven guidelines were identified through a systematic literature review. Details of the source, approach, risk categories, use of lipid serum concentrations and recommendations for treatment were extracted.

In addition, a number of publications on comparison of the international guidelines were identified and studied to inform the outcomes of this review[[30]](#endnote-31),[[31]](#endnote-32),[[32]](#endnote-33),[[33]](#endnote-34),[[34]](#endnote-35).

For additional details and a more comprehensive review of the evidence gathered to inform TOR 2, refer to the Review of Clinical Guidelines undertaken by the CPHR, Deakin **(Appendix G).**

### 2.2.2 Comparison of Australian and international treatment guidelines

All current guidelines recommend treatment based on an individual patient’s risk of having a cardiovascular event.

Guidelines separate patients into one of two groups: 1) patients who have not had a cardiovascular event (primary prevention); and 2) those who have had a cardiovascular event (secondary prevention). Within each group, guidelines link treatment to the presence of a number of risk factors that have been identified though large epidemiological studies such as the Framingham Study.

All of the guidelines use an absolute risk approach. Absolute risk is the probability of a cardiovascular event occurring. The absolute risk can sometimes be modified by changing exposure to factors that are associated with cardiovascular disease. Modifiable risk factors include reducing serum lipid concentrations, smoking cessation and increased physical activity. Some risk factors are not modifiable e.g. age and gender.

Each guideline derives an assessment of the risk of cardiovascular disease for a patient based on algorithms that apply the absolute risk from epidemiological studies with patient specific inputs. The equations used differ between the various guidelines and the patient information also varies. For example, some guidelines use a 10 year risk of an event and others 5 years. Most calculations require the serum LDL-C concentration measurement to be entered into the algorithm. The Australian NVDPA-2012 guidelines list target concentrations for a wide range of lipid measures (LDL-C, triglycerides, HDL-C, total cholesterol).

The calculated risk of having a cardiovascular event will vary according to which guidelines and absolute risk calculator are used. Each calculator assigns a patient to a “risk category”. The number of categories varies from two to five.

There are three Australian guidelines for clinicians who treat patients at an elevated risk of cardiovascular events. These are: the NVDPA-2012 which focuses on primary prevention; the National Heart Foundation *Reducing Risk in Heart Disease* guideline (NHF-2012) focusing on secondary prevention; and the Cardiac Society of Australia and New Zealand (CSANZ) *Guidelines for the Diagnosis and Management of Familial Hypercholesterolaemia*.

### 2.2.3 Approaches to therapeutic treatment in the guidelines

Treatments to lower non-HDL-C serum concentrations include diet, lifestyle modification and pharmacotherapies. Recommendations are linked to the patient’s risk of an event. Where patients have a high risk of an event, commencing pharmacotherapy immediately is recommended. Statins are universally recommended as first line therapy.

Where, in spite of maximum tolerated doses of statin therapy, the lipid concentration needs to be further reduced, additional treatment is recommended. Categories of patients for whom additional treatment is considered necessary include those who: have increased the statin dose to the maximum level tolerable; are contraindicated to statins; or are no longer responding to treatment. Ezetimibe is one of the choices of non-statin therapies for these patient groups.

Guidelines vary when ezetimibe is the optimal treatment choice. For example, some guidelines restrict the use of ezetimibe plus a statin to higher risk groups, whereas the NVDPA-2012 guidelines position ezetimibe as second line when LDL-C serum concentrations are not sufficiently reduced on maximally tolerated doses of a statin. The NHF-2012 guidelines recommend that all patients who have coronary heart disease should be treated with a statin; but also recommend ezetimibe as monotherapy or in combination with a statin. That is, the NHF-2012 guidelines do not explicitly position ezetimibe as a second line therapy.

The approach to treatment to prevent cardiovascular events is similar across the identified guidelines. The variation between guidelines reflects differences in: baseline absolute risk in each country; which risk values are used (five year or ten year); and the approach to which pharmacotherapy is preferred where further reduction in lipids is required.

### 2.2.4 Recently published literature

In addition to the CHPR review of clinical guidelines, the Reference Group considered a number of additional, more recent research papers relevant to the Review. The study by Bohula et al[[35]](#endnote-36) defines subgroups of IMPROVE-IT participants who benefitted most from ezetimibe. Those who showed significant benefit from ezetimibe/statin therapy were in the highest cardiovascular risk category i.e. the secondary prevention group with three or more additional risk factors. This reconfirms ezetimibe’s place in therapy as second line to statins and in patients with highest risk. For further details on this study refer to TOR 3.

A sub group analysis of the IMPROVE-IT trial in high risk patients[[36]](#endnote-37) and accompanying editorial[[37]](#endnote-38) also suggests that benefit from ezetimibe is restricted to those with high risk in a secondary prevention population; in this case, those with prior CABG and acute coronary syndrome. Patients with prior CABG received significantly greater benefit from treatment with ezetimibe in addition to simvastatin compared to those without prior CABG (Absolute Risk Reduction of 8.8% versus 1.3%).

A recently published paper by Yang et al[[38]](#endnote-39) also supports benefit of statin/ezetimibe combination therapy in those patients with high risk. This study enrolled 245 patients with high or moderately high risk of CVD as defined by the National Cholesterol Education Program Adult Treatment Panel 3. Patients received one of six rosuvastatin monotherapy or rosuvastatin/ezetimibe combination regimens for eight weeks. The proportion of patients with adverse events was not significantly different between the monotherapy and combination therapy groups. The combination therapy lowered LDL-C concentrations and achieved the LDL-C target in patients with high cardiovascular risk.

### 2.2.5 Australian guidelines compared to the PBS GSLLD

In examining the differences between the NVDPA-2012 and the GSLLD, the Reference Group noted that the purpose of each document is different. The NVDPA-2012 provides guidance for therapy, including pharmacotherapy, in individual patients at risk of CVD. The GSLLD is constructed from sequential considerations of evidence of relative effectiveness and cost-effectiveness considered by the PBAC for the purposes of subsidy on the PBS.

The GSLLD and NVDPA-2012 guidelines are broadly consistent in terms of the risk factors that are considered prior to commencing treatment. The main differences are:

* Target concentrations of LDL-C, triglycerides and HDL-C that provide thresholds for commencing pharmacotherapy are slightly different. The serum lipid concentrations form one part of the absolute risk categorisation. Some patients could be eligible for subsidised drugs because of their serum lipids when considered in isolation, but would not be eligible according to their calculated risk. Conversely, some patients have higher risk according to the NVDPA-2012, but do not have dyslipidaemia[[39]](#endnote-40).
	+ Whilethe actual numbers have not been examined in any published study, in their comparison of eligibility for pharmacotherapy in a cohort of 3,627 subjects from the AusDiab study (2004-5)[[40]](#endnote-41), 2% of patients would be eligible for treatment in spite of having normal blood pressure and LDL-C serum concentrations.
* The GSLLD does not include consideration of chronic kidney disease (CKD) as a risk factor. The other factors considered in NVDPA-2012 are present in the GSLLD.
* The GSLLD does not include a consideration of age while the NVDPA-2012 is recommended for the age range of 35 – 75 years.

Table 11 shows additional details of the comparison between the GSLLD and NVDPA-2012.

Table 11: Discrepancies in risk factors corresponding to the high risk of a CVD event

|  |  |  |
| --- | --- | --- |
| **Risk factor** | **Included in GSLLD** | **Included in NVDPA-2012** |
| Moderate or severe CKD | No | Yes |
| Family history of coronary heart disease (CHD) which has become symptomatic before the age of 55 years in two or more 1st degree relatives | yes | Not explicitly, but carries additional weight in the calculation of a cardiovascular risk with a web calculator or a chart  |
| Family history of CHD which has become symptomatic before the age of 45 years in one or more 1st degree relatives | Yes | Not explicitly, but carries additional weight in the calculation of a cardiovascular risk with a web calculator or a chart |
| Previous diagnosis of familial hypercholesterolaemia | Yes, conditional on the specified threshold in cholesterol level as in Table 2.4. | Yes, unconditionally^ |
| Systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg | Patients with hypertension (without specified thresholds) need to meet the specified cholesterol level thresholds as in Table 2.4. | Yes, unconditionally |
| Serum total cholesterol >7.5mmol/L | No, except for males aged 35-75 years and post-menopausal women as in Table 2.4. | Yes, unconditionally |

^consistent with guidelines identification and management of familial hypercholesterolaemia (Table A2.1 in appendix)

Source: Table 2.2, p16 of the CPHR report

There are small differences between the eligibility of patients for pharmacotherapy between the GSLLD and Australian guidelines for treatment. The effect of these differences has not been quantified, with one study indicating that it may not be substantial[[41]](#endnote-42). This study indicated that using individual factors to determine eligibility rather than the absolute risk calculator showed some under-treatment of high risk patients and some over-treatment of lower risk patients.

## 2.3 Key issues raised by stakeholders on TOR 2

Details of the submissions to the Review are provided in **Appendix H**.

### 2.3.1 Submissions to the Review

In the seven week public consultation held between 4 March and 22 April 2016 stakeholders raised the following key points in relation to TOR 2:

* Clinical management guidelines for reducing cardiovascular disease and its consequences include consideration of dyslipidaemia and other risk factors.
* LDL-C is increasingly recognised as the primary lipid treatment target in patients with high cardiovascular risk. LDL-C treatment targets to be achieved through pharmacotherapy have become progressively lower over time.
* There may be differences between approaches to treatment in hospital and the community. The current guidelines are generally consistent with the GSLLD on the PBS.
* Some overseas guidelines, namely those from the American College of Cardiology and the American Heart Association, have been recently revised to recommend the additional use of non-statin cholesterol-lowering medicines such as ezetimibe to high risk patients who do not reach targets with statins alone.

### 2.3.2 Outcomes from the stakeholder forum

At the stakeholder forum, the Reference Group was interested in stakeholders’ views on why ezetimibe should be positioned as second line therapy through PBS restrictions. A recent systematic review and meta-analysis (Silverman et al[[42]](#endnote-43)) suggests that the order of LLT used to achieve a reduction in LDL-C is not important in reducing patients’ risk of cardiovascular events. Comments made by participants in relation to this question included:

* its use is supported by internationally-accepted standards and guidelines
* the Silverman et al[[43]](#endnote-44) paper showed that lowering LDL–C resulted in a greater reduction of risk; it did not discuss the ordering of the medicines used in treatment
* recent European and American (USA) guidelines promoting the current hierarchy in treatment – that is, ezetimibe used as second line therapy – 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 listing.

Participants were asked whether the GLSSD is still relevant and if so, should it be revised. Participants noted that while the General Statement did not explicitly refer to ezetimibe, it did cross-reference the ezetimibe PBS restrictions, and the PBS restrictions do not fully reflect prescribing practice. While it was suggested that the General Statement remains relevant, it was further noted that PBS restrictions are based on the outcomes of the PBAC’s cost-effectiveness deliberations (which is a legislative requirement of the *National Health Act 1953*). This can result in some differences between PBS restrictions and clinical guidelines. Some participants commented that the General Statement is complicated and revision may be beneficial.

The [Stakeholder Forum Outcome Statement](http://www.pbs.gov.au/reviews/ezetimibe-review-files/ezetimibe-stakeholder-forum-outcomes-report.pdf) is available on the Review website and at **Appendix F**. Stakeholder responses to the Stakeholder Forum Outcome Statement are available on the Review’s [Public Consultation website](http://www.pbs.gov.au/info/reviews/ezetimibe-review-public-consultation).

### 2.3.3 Stakeholder submissions to the draft Report

Stakeholders raised the following points in their responses to the draft Report provided on the PMR website from 30 January to 10 February 2017.

* Ezetimibe has an established and important role in clinical practice. Ezetimibe remains essential for treating patients who are unable to tolerate increasing doses of statins, have high baseline cardiovascular event risk, or are unable to take statins at all.
* A number of submissions expressed approval at reducing ezetimibe to a Restricted Benefit listing on the PBS, but one submission considered the current Authority Required listing remains appropriate to support the place of ezetimibe as second line therapy.
* The PBS GSLLD should be removed for statins.

## 2.4 Reference Group consideration

The Reference Group noted that all current treatment guidelines for management of hypercholesterolaemia recommend the use of statins as first line pharmacotherapy to lower LDL-C concentrations. Two guidelines released in 2016 continue to support this approach:

* 2016 American College of Cardiology (ACC) *Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk*
* 2016 European Society of Cardiology / European Atherosclerosis Society (EAS) *Guidelines for the Management of Dyslipidaemias*

This is due to the quality and volume of clinical evidence available that indicate that lowering LDL-C by statins translates to a reduction in risk of cardiovascular events. Ezetimibe is placed after statins on the basis of the limited data available, with only one trial (IMPROVE-IT) showing outcome data. IMPROVE-IT demonstrates a reduction in LDL-C by ezetimibe lowers CV risk as predicted and there are no toxicity signals. However, IMPROVE-IT included a specific secondary prevention population that may not reflect the population of patients being treated under the current Australian guidelines. Therefore, there are some limitations with the generalisability of the results.

The Reference Group accepted that a reduction in LDL-C is a valid surrogate for measuring reduction of CV risk for both ezetimibe and statins. The initial use of statins and up-titration of statins prior to using ezetimibe should be promoted. When using pharmacotherapy to lower LDL-C the choice of therapy is dependent on clinical preference. However, the Reference Group noted that guidelines generally recommend statins as the initial therapy, reserving other LLT including ezetimibe for second line therapies, as noted above.

As noted previously (TOR 1, section 1.3.3) the sponsor’s response to the draft Report stated that prescribers and patients place significant value on ezetimibe’s ability to lower LDL-C and event risk without increasing the likelihood of adverse effects associated with higher statin doses (MSD response to the draft Report, p.2). This further reinforced the Reference Group’s view that there is a significant patient population for whom ezetimibe is added to statin therapy before maximum tolerated doses of statins are trialled.

The Reference Group noted from recent literature that diagnosing true statin-associated muscle symptoms is difficult. Whether statins cause muscle symptoms with no or only mild creatinine kinase elevations is irrelevant, as if a patient believes statins are responsible it is difficult to convince them otherwise[[44]](#endnote-45). The incidence of statin myalgia has been estimated at 10% from observational studies[[45]](#endnote-46).

Cohen et al suggests that whilst statins are well tolerated, statin associated adverse effects are clinically important. Statin associated muscle side-effects are reported by 10-25% of patients taking statin therapies[[46]](#endnote-47).

The Reference Group considered that whilst ezetimibe is one of the treatment options for patients in whom statin therapy is contraindicated or not tolerated, strategies for managing statin intolerance include prescribing a different statin, taking a treatment break and rechallenging, or reducing the dose of statin.

All guidelines take an absolute risk reduction approach. This means that multiple measurable factors are taken into account, the sum of which lead to a categorisation of the risk of a CV event over a specified time period (either 5-year or 10-year period depending on the guidelines). The GSLLD uses an absolute risk over a 15 year period as its basis and commencing treatment with a LLT depends more on consideration of individual risk factors. The Reference Group noted that since the inception of the GSLLD, clinical management of CV risk has developed with more research into risk factors. An example of the differences in approach between the GSLLD and an absolute risk calculator approach is found in patients with primary prevention. Whereas most clinicians would commence patients on a LLT at total cholesterol concentrations lower than the 9 mmol/L threshold, depending on risk factors, the GSLLD limits initiation of treatment for patients not otherwise included in other categories to this high threshold.

The Reference Group discussed the role of PBS restrictions and acknowledged the importance of PBS restrictions being contemporary and not obstructing clinical guidelines. In a number of therapeutic areas, e.g. oncology, the PBS restrictions place therapies as second and third line on the basis of clinical trial data providing evidence of comparative clinical effectiveness and cost-effectiveness in later line therapy. However, this is not the case for ezetimibe. Ezetimibe is placed second line in the clinical guidelines because clinicians generally have more confidence in the quality and quantity of trial data showing improved health outcomes underpinning use of statins. Studies identified in this review show that statins reduce baseline LDL-C by 30%-50% in contrast to ezetimibe which achieves an 18% reduction.

The Reference Group considered there were a number of reasons supporting making statins unrestricted on the PBS. These include substantial reductions in statin price, providing support for use of statins when initiating pharmacotherapy, and the mature market. Placing ezetimibe as a Restricted Benefit may send a message to prescribers that the PBS does consider it second line to statins. The existing Authority Required (Streamlined) listing of ezetimibe as second line therapy is also compatible with clinical guidelines.

The Reference Group considered that the statin market is now mature and that the GSLLD does not reflect contemporary use of LLT. The PBAC may wish to consider removing the GSLLD since the use of LLT is now firmly established in well publicised guidelines and the recommended approach used by clinicians to CV risk reduction is well founded in evidence.

The DUSC agreed that the statin market is mature and that Australia’s statin use (DDD/1000 population/day) is one of the highest of all OECD countries[[47]](#endnote-48). The DUSC also agreed that any relaxation of the PBS statin restriction is unlikely to substantially change the utilisation of statins.

DUSC considered the utilisation of ezetimibe is still growing, particularly FDC use with statins. The following graph (Figure 2) reaffirms the DUSC’s position that ezetimibe use is growing. The DUSC also considered relaxing the restriction would further grow the ezetimibe market and potentially increase use in the population where cost-effectiveness is uncertain i.e. those patients who have not been treated with maximally tolerated doses of statins prior to initiating ezetimibe. Retaining an Authority Required (Streamlined) listing would reflect the evidence that ezetimibe should remain second line therapy to statins for hypercholesterolaemia.

Figure 2: RPBS/PBS prescriptions for ezetimibe 1 July 2011 - 31 December 2016

PBS Information Product, DUSC Database accessed 5 April 2017

Removal of the GSLLD would require revision of the ezetimibe restrictions, as for most patients, access to PBS subsidised ezetimibe requires a trial of statin therapy. The Reference Group provided a possible revised restriction for ezetimibe. In making this recommendation, the Reference Group acknowledged successful implementation will require education to promote the importance of absolute risk reduction in the approach to CV disease management. The Reference Group also noted that the Australian Risk Calculator[[48]](#endnote-49) is used by prescribers to calculate an individual’s risk of CV events but is not validated to monitor or quantify risk reduction following commencement of LLT. The PBAC may wish to apply a contemporary absolute risk threshold approach to the ezetimibe restriction.

The Reference Group considered the criterion ‘treatment must be in conjunction with dietary therapy and exercise’ could be removed as there was little evidence supporting the interaction between diet/exercise and cholesterol reduction but acknowledged the benefits of such interventions in CV risk reduction, e.g. weight reduction and blood pressure lowering.

The Reference Group considered that changing restrictions presented an educational opportunity. Opportunities should be sought to promote the message that for quality use of medicines, optimal management of LDL-C reduction requires statins be first choice. Compliance with therapy is essential in order to ensure that optimal health benefit is achieved. Ezetimibe should only be prescribed after the statin dose has been optimised, unless the patient is contraindicated to statin therapy.

The PBAC may wish to consider the following revised restrictions for ezetimibe. In the future, the PBAC may wish to apply a contemporary absolute risk threshold approach to the PBS ezetimibe restriction for both the high and low CV risk populations.

### 2.4.1 Suggested ezetimibe restrictions

**Ezetimibe 10 mg**

**Authority Required (Streamlined)**

**Hypercholesterolaemia**

Clinical Criteria

* The treatment must be co-administered with an HMG CoA reductase inhibitor (statin)

**AND**

* Patient must have cholesterol concentrations that are inadequately controlled with an HMG CoA reductase inhibitor (statin). Inadequate control is a cholesterol concentration in excess of 4mmol per L after at least 3 months of treatment at a maximum tolerated dose of a statin. The dose and duration of statin treatment and the cholesterol concentration which shows inadequate control must be documented in the patient’s medical records when ezetimibe is initiated.

**AND**

* Patient falls into at least one of the very high risk categories described as:
1. coronary heart disease which has become symptomatic
2. cerebrovascular disease which has become symptomatic
3. peripheral vascular disease which has become symptomatic
4. diabetes mellitus with microalbuminuria (defined as urinary albumin excretion rate of >20mcg/min or urinary albumin to creatinine ratio of > 2.5 for males, > 3.5 for females)
5. diabetes mellitus in Aboriginal or Torres Strait Islander patients
6. diabetes mellitus in patients aged 60 years or more
7. family history of coronary heart disease which has become symptomatic before the age of 55 years in two or more first degree relatives
8. family history of coronary heart disease which has become symptomatic before the age of 45 years in one or more first degree relatives
9. heterozygous/homozygous familial hypercholesterolaemia.

**OR**

* Where a patient’s level of absolute risk of a cardiovascular event is greater than 15% over 5 years as calculated by the Australian Absolute cardiovascular disease risk calculator (National Vascular Disease Prevention Alliance).

**Ezetimibe 10mg**

**Authority Required (Streamlined)**

**Hypercholesterolaemia**

Clinical criteria

* + Patient must be one in whom treatment with an HMG CoA reductase inhibitor (statin) is contraindicated.

**AND**

* Patient falls into a very high risk category described as:
1. coronary heart disease which has become symptomatic
2. cerebrovascular disease which has become symptomatic
3. peripheral vascular disease which has become symptomatic
4. diabetes mellitus with microalbuminuria (defined as urinary albumin excretion rate of >20mcg/min or urinary albumin to creatinine ratio of > 2.5 for males, > 3.5 for females)
5. diabetes mellitus in Aboriginal or Torres Strait Islander patients
6. diabetes mellitus in patients aged 60 years or more
7. family history of coronary heart disease which has become symptomatic before the age of 55 years in two or more first degree relatives
8. family history of coronary heart disease which has become symptomatic before the age of 45 years in one or more first degree relatives
9. heterozygous/homozygous familial hypercholesterolaemia.

**OR**

* Where a patient’s level of absolute risk of a cardiovascular event is greater than 15% over 5 years as calculated by the Australian Absolute cardiovascular disease risk calculator (National Vascular Disease Prevention Alliance).

**Ezetimibe 10mg**

**Authority Required (Streamlined)**

**Hypercholesterolaemia**

Clinical criteria

* + Patient must have developed a clinically important product-related adverse event during treatment with an HMG CoA reductase inhibitor (statin) necessitating a reduction in statin dose. The type and severity of the adverse event must be documented in the patient’s medical records **OR**
	+ Patient must have developed a clinically important product-related adverse event during treatment with an HMG CoA reductase inhibitor (statin) necessitating a withdrawal of the statin treatment. The type and severity of the adverse event must be documented in the patient’s medical records

**AND**

* Patient falls into a very high risk category described as:
1. coronary heart disease which has become symptomatic
2. cerebrovascular disease which has become symptomatic
3. peripheral vascular disease which has become symptomatic
4. diabetes mellitus with microalbuminuria (defined as urinary albumin excretion rate of >20mcg/min or urinary albumin to creatinine ratio of > 2.5 for males, > 3.5 for females)
5. diabetes mellitus in Aboriginal or Torres Strait Islander patients
6. diabetes mellitus in patients aged 60 years or more
7. family history of coronary heart disease which has become symptomatic before the age of 55 years in two or more first degree relatives
8. family history of coronary heart disease which has become symptomatic before the age of 45 years in one or more first degree relatives
9. heterozygous/homozygous familial hypercholesterolaemia.

**OR**

* Where a patient’s level of absolute risk of a cardiovascular event is greater than 15% over 5 years as calculated by the Australian Absolute cardiovascular disease risk calculator (National Vascular Disease Prevention Alliance)

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

1. Severe myalgia (muscle symptoms without creatine kinase elevation) which is proven to be temporally associated with statin treatment; or
2. 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
3. Unexplained, persistent elevations of serum transaminases (greater than 3 times the upper limit of normal) during treatment with a statin.

**Ezetimibe 10mg**

**Authority Required (Streamlined)**

**Hypercholesterolaemia**

Clinical Criteria

* + Homozygous sitosterolaemia.

**Ezetimibe in combination with statin**

**Authority Required (Streamlined)**

**Hypercholesterolaemia**

Clinical Criteria

* Patient must have cholesterol concentrations that are inadequately controlled with an HMG CoA reductase inhibitor (statin). Inadequate control is a cholesterol concentration in excess of 4mmol per L after at least 3 months of treatment at a maximum tolerated dose of a statin. The dose and duration of statin treatment and the cholesterol concentration which shows inadequate control must be documented in the patient’s medical records when ezetimibe is initiated.

**AND**

* Patient falls into at least one of the very high risk categories described as
1. coronary heart disease which has become symptomatic
2. cerebrovascular disease which has become symptomatic
3. peripheral vascular disease which has become symptomatic
4. diabetes mellitus with microalbuminuria (defined as urinary albumin excretion rate of >20mcg/min or urinary albumin to creatinine ratio of > 2.5 for males, > 3.5 for females)
5. diabetes mellitus in Aboriginal or Torres Strait Islander patients
6. diabetes mellitus in patients aged 60 years or more
7. family history of coronary heart disease which has become symptomatic before the age of 55 years in two or more first degree relatives
8. family history of coronary heart disease which has become symptomatic before the age of 45 years in one or more first degree relatives
9. heterozygous/homozygous familial hypercholesterolaemia.

**OR**

* Where a patient’s level of absolute risk of a cardiovascular event is greater than 15% over 5 years as calculated by the Australian Absolute cardiovascular disease risk calculator (National Vascular Disease Prevention Alliance)

**Ezetimibe in combination with statin**

**Authority Required (Streamlined)**

**Hypercholesterolaemia**

Clinical criteria

* + Patient must have developed a clinically important product-related adverse event during treatment with an HMG CoA reductase inhibitor (statin) necessitating a reduction in statin dose. The type and severity of the adverse event must be documented in the patient’s medical records.

**AND**

* Patient falls into a very high risk category described as
1. coronary heart disease which has become symptomatic
2. cerebrovascular disease which has become symptomatic
3. peripheral vascular disease which has become symptomatic
4. diabetes mellitus with microalbuminuria (defined as urinary albumin excretion rate of >20mcg/min or urinary albumin to creatinine ratio of > 2.5 for males, > 3.5 for females)
5. diabetes mellitus in Aboriginal or Torres Strait Islander patients
6. diabetes mellitus in patients aged 60 years or more
7. family history of coronary heart disease which has become symptomatic before the age of 55 years in two or more first degree relatives
8. family history of coronary heart disease which has become symptomatic before the age of 45 years in one or more first degree relatives
9. heterozygous/homozygous familial hypercholesterolaemia.

**OR**

* Where a patient’s level of absolute risk of a cardiovascular event is greater than 15% over 5 years as calculated by the Australian Absolute cardiovascular disease risk calculator (National Vascular Disease Prevention Alliance).

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 3 times the upper limit of normal) during treatment with a statin.

# Section 3: TOR 3Clinical and cost-effectiveness of ezetimibe

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.

## 3.1 Key findings for TOR 3

### 3.1.1 Evidence review on the clinical effectiveness of ezetimibe

The Literature Review sought to identify recent clinical studies of ezetimibe reporting on long-term patient relevant outcomes. One study was identified that reported patient relevant outcomes, the IMPROVE-IT trial, and was considered alongside other evidence on the effect of ezetimibe on LDL-C lowering to inform the Review’s response to TOR 3. No trials were identified that reported on patient relevant outcomes in those treated with ezetimibe monotherapy.

* There was insufficient clinical trial evidence in addition to that previously considered by the PBAC, available to assess whether adding ezetimibe to the maximum tolerated dose of a statin, compared to a placebo plus maximum tolerated dose of a statin was associated with: superior long-term outcomes of survival; quality–adjusted survival; fatal and non-fatal CV events; or superior surrogate outcomes i.e. lipid endpoints including total cholesterol (TC), LDL-C, and HDL-C.
* There was one study of long-term outcomes that is applicable to a subset of the Australian population. IMPROVE-IT[[49]](#endnote-50) was conducted in a secondary prevention population that assessed long-term patient outcomes associated with the addition of ezetimibe 10 mg to simvastatin 40 mg versus simvastatin 40 mg plus placebo.
* The clinical outcomes of IMPROVE-IT confirm the acceptability of the absolute reduction in LDL-C as a valid surrogate for the reduction of the relative risk of major vascular events in patients receiving ezetimibe. The reduction in cardiovascular event rate was as predicted by the known relationship between absolute reduction in LDL-C and the relative risk reduction. Clinical outcomes from the IMPROVE-IT trial are the first to justify the role of ezetimibe as a non-statin LLT option for the reduction of cardiovascular risk.
* On the basis of IMPROVE-IT outcomes, long-term use of ezetimibe appears to be safe.
* The IMPROVE-IT study enrolled a trial population which does not meet the PBS eligibility criteria for subsidised prescription of ezetimibe. Patients were treated with fixed doses of simvastatin with no up-titration to maximally tolerated doses or switch to statin of a higher potency as required by the current PBS restriction for ezetimibe. The study population was restricted to the secondary prevention population, i.e. patients who had been hospitalised for an acute coronary syndrome in the preceding 10 days.
* For ezetimibe monotherapy, results of the meta-analyses of eight randomised controlled trials (nine for HDL-C results) reported in the systematic review by Pandor[[50]](#endnote-51), and confirmed by the independent assessment conducted for this review, indicate that ezetimibe monotherapy reduced LDL-C concentrations by approximately 20% from baseline compared with placebo. By comparison, statins, depending on dose and potency, reduce LDL-C by at least 30-50% from baseline. None of the trials included in the meta-analyses enrolled patients with confirmed statin intolerance or contraindication to statin therapy.
* It is acknowledged that ezetimibe and statins have independent mechanisms of action. However, the dose of ezetimibe is fixed whereas with statins there is the capacity to up-titrate the potency or dose. While the LDL-C lowering capacity of statins does plateau with increasing dose, the greatest absolute reduction in LDL-C (and CV risk reduction) can be achieved with use of higher doses of statins prior to adding ezetimibe. Therefore, the magnitude of the absolute reduction in LDL through the addition of ezetimibe is dependent on the LDL-C concentration following treatment with maximum tolerated doses of statin.
* The greater absolute reduction in LDL achieved by most strengths and types of statins support statins as first line therapy for hypercholesterolaemia. For patients who are contraindicated or cannot tolerate higher statin doses, ezetimibe will provide additional benefits that could not otherwise be achieved.
* Ezetimibe monotherapy appeared to be well tolerated with a safety profile similar to placebo.
* The results of the Bohula et al[[51]](#endnote-52) analysis of IMPROVE-IT showed significant benefit of ezetimibe/statin combination therapy only in those patients with very high cardiovascular risk. This underlines the importance of restricting use of ezetimibe to second line therapy following optimal use of statins and in those patients with very high risk.
* The limited clinical evidence on long-term patient relevant outcomes and lack of applicability to the PBS population casts uncertainty over cost-effectiveness of ezetimibe in combination with statin versus maximally tolerated statin.

### 3.1.2 Review of the Economic Modelling of Ezetimibe

* The base case Incremental Cost-Effectiveness Ratio (ICER) presented in the sponsor’s submission is considered uncertain. This is because the approach used for extrapolating the benefits beyond the period of the trial follow-up is likely to have overestimated the incremental long-term benefits associated with a combination of ezetimibe and a statin.
* The evidence reporting on long-term patient relevant outcomes casts uncertainty over the cost-effectiveness of ezetimibe in combination with statin versus statin monotherapy. This arises from the sensitivity of the ICER to the estimates of clinical efficacy in terms of TC:HDL ratio provided in the sponsor’s submission and those derived during the PMR. Alternative efficacy estimates were obtained for a sensitivity analysis from the meta-analysis of trials that enrolled primary, secondary or mixed prevention populations. When these results were used as input to the model (reduction in TC:HDL ratios of -18.84% versus -9.65% in ezetimibe and comparator arms, respectively) rather than the sponsor’s estimates, the base case ICER almost doubled across all time horizons.
* An economic model based on the results of the IMPROVE-IT trial would not provide a reasonable estimate of the cost-effectiveness of current ezetimibe use on the PBS due to applicability issues.
* The Reference Group agreed that in considering the cost-effectiveness of ezetimibe the comparators include:
	+ placebo/non statin LLT for those patients contraindicated to statins; and
	+ up-titration of statin to maximum tolerated dose/switching to a higher potency statin.

## 3.2 Evidence review on the clinical effectiveness of ezetimibe

The full systematic Literature Review prepared by the CPHR, Deakin, is provided at **Appendix I.**

### 3.2.1 Summary of the PBAC consideration and listing history

A review of the PBS listing history of ezetimibe and ezetimibe/statin combination products is presented in the Systematic Literature Review (**Appendix I**).

### 3.2.2 Systematic Literature Review

The literature search identified all randomised controlled trials (RCTs) or meta-analyses that evaluated the effect of ezetimibe as monotherapy or in combination with a statin.

The major databases including MEDLINE, EMBASE, and Cochrane databases were searched to identify peer-reviewed publications relating to ezetimibe in treating adult patients with familial or non-familial hypercholesterolemia. Registries of RCTs, sponsors’ PBAC submissions and PBAC commentaries were searched. A manual search of reference lists of all relevant publications was undertaken. The [Clinical Trial Registry](https://clinicaltrials.gov/ct2/home) was accessed to identify any registered and completed phase III or IV clinical trials involving ezetimibe for treatment of hypercholesterolaemia. Selection criteria are presented in the Literature Review, Table 2.2.1, p 9 (**Appendix I**).

The search identified 14 publications presenting results of 11 systematic reviews, and 62 publications that provided results from 30 RCTs.

### 3.2.3 Recently published literature

In addition to the published evidence in the CPHR Literature Review, the Reference Group considered recently published literature[[52]](#endnote-53),[[53]](#endnote-54),[[54]](#endnote-55),[[55]](#endnote-56) to inform the response to TOR 3. In particular, the Reference Group sought information on the costs and uncertainties around the benefits of adding non-statin LLTs to statin therapy, the ordering of LLT, and the cost-effectiveness of a more aggressive approach in lowering baseline LDL-C concentrations.

The Reference Group noted a recently published study (Bohula et al[[56]](#endnote-57)), which was an analysis of the IMPROVE-IT trial. The study tested the hypothesis that atherothrombotic risk stratification may be useful to identify post-acute coronary syndrome (ACS) patients who have the greatest potential for benefit from the addition of ezetimibe to statin therapy. The study used the TIMI (Thrombolysis In Myocardial Infarction) Risk Score for Secondary Prevention (TRS2ºP), a 9 point stratification tool previously developed in a large population with atherothrombosis to predict CV death, myocardial infarction (MI), and ischaemic stroke. The TRS2ºP risk indicators were congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, prior stroke, prior coronary artery bypass graft, peripheral artery disease, eGFR less than 60 mL/min, and smoking. The tool was applied prospectively to 17,700 (IMPROVE-IT) post-ACS patients randomised to ezetimibe + simvastatin or simvastatin + placebo. Treatment efficacy was assessed by baseline risk for CV death/MI/ischaemic stroke, the IMPROVE-IT composite endpoints, and individual component endpoints at 7 years.

All nine clinical variables in the TRS2ºP were independent risk indicators for CV death/MI/ischaemic stroke. The integer based scheme showed a strong graded relationship with the rate of CV death/MI/ischaemic stroke, the trial composite endpoints and the individual components. The paper concluded atherothrombotic risk stratification using the TRS2ºP identifies high risk patients who derive greatest benefit from the addition of ezetimibe to statin therapy for secondary prevention following ACS. High risk patients (those with three or more risk indicators) had an absolute risk reduction of 6.3%, (95% CI: 2.9%-9.7%). Intermediate risk patients (two risk indicators) had a 2.2% absolute risk reduction, whilst low risk patients (nil to one risk factor) showed no benefit from the addition of ezetimibe.

This observation, together with the fact that IMPROVE-IT is the only clinical trial showing patient relevant outcomes (however no mortality benefit), that clinical guidelines continue to place ezetimibe second line, and that ezetimibe lowers LDL-C concentrations less than statins, all underline the importance of restricting use of ezetimibe to second line therapy following optimal use of statins in those patients with very high risk.

### 3.2.4 Clinical efficacy and safety of ezetimibe as monotherapy and in combination with a statin

There were no identified published meta-analyses of reasonable quality of ezetimibe, either as monotherapy or added to the maximum tolerated dose of statin, that showed that the addition of ezetimibe is associated with improved patient relevant outcomes of mortality, acute coronary events and revascularisation procedures.

The two systematic reviews in populations with a high risk of cardiovascular disease, undertaken by the Agency for Healthcare Research and Quality in the USA, identified 40 RCTs comparing ezetimibe co-administered with a statin to a more intense statin therapy. The intensity of statin was based on comparisons of the doses (Refer to **Appendix I**, Literature Review, Table 2.2.3.2, p 20). The authors[[57]](#endnote-58) found high levels of heterogeneity between the studies which limited the analysis. The percentage reduction in LDL-C was strongly influenced by the intensity of the statin dose combined with ezetimibe and in the comparator arm of the study.

When the study population was limited to people with pre-existing CV disease (secondary prevention population), the addition of ezetimibe to a mid-intensity statin provided participants with a 5-15% greater reduction in LDL-C than a high potency statin in the majority of studies. It was not possible to combine the results of the studies due to heterogeneity.

In a meta-analysis of six studies which compared adding ezetimibe to a statin, to doubling the statin dose, the addition of ezetimibe showed statistically significant change in LDL-C (weighted mean difference -15.3%; 95% CI -19.1, -11.4) but there was substantial heterogeneity associated with the trial design, duration, dose and type of statin which results in low confidence in the extent of difference[[58]](#endnote-59).

In a meta-analysis commissioned by National Institute for Health Care and Excellence (NICE) (2008), six RCTs were meta-analysed[[59]](#endnote-60). These compared adding ezetimibe to a statin compared to the same dose of statin. This meta-analysis showed that the addition of ezetimibe statistically significantly improved LDL-C reduction and total cholesterol.

There were no identified published trials investigating the effect of initiating LLT with ezetimibe and then adding a statin.

### 3.2.5 Applicability issues

The populations in many studies that add ezetimibe to a statin may not meet the restriction criteria for PBS subsidy, with the exception of the Health Technology Assessment (HTA) 2015 review by NICE[[60]](#endnote-61). The people in many of these studies were inadequately managed on the statin dose alone but these trials did not usually specify that the statin dose should be the maximum tolerated, which is the requirement of the current PBS restriction.

These results support two options for clinicians seeking to further reduce LDL-C in patients in secondary prevention: 1) increasing the dose or intensity of the statin; or 2) adding ezetimibe to a low dose statin. It is not clear from the evidence presented and the relevant guidelines that prescribers currently seek to increase the statin dose to that maximally tolerated by the patient in every case. The choice is likely to depend on individual patient factors.

IMPROVE-IT[[61]](#endnote-62) was the only RCT designed to assess long-term patient outcomes that met the selection criteria. It assessed clinical efficacy and safety of ezetimibe plus simvastatin vs placebo plus simvastatin in a secondary prevention population who had been hospitalised for an acute coronary syndrome within the preceding 10 days. Issues associated with the applicability of results from IMPROVE-IT to the target population for the PBS were identified, including:

* the IMPROVE-IT patient population baseline LDL-C concentration was set at 1.3 to 2.43 mmol/L
* at the time of enrolment only 34% of patients were being treated with a statin
* for other patients, ezetimibe in combination with simvastatin was prescribed as the first line treatment
* there was no evidence that patients who had been treated with statins prior to randomisation were at their maximum tolerated dose.

Therefore, IMPROVE-IT enrolled a population that did not meet the eligibility criteria for PBS subsidised ezetimibe as:

* the population was a secondary prevention cohort
* patients may not have been taking maximum tolerated dose of a statin as required by the PBS restriction and ezetimibe was added to a fixed dose of simvastatin
* the baseline LDL-C ranged between 1.3 and 2.43 mmol/L, whereas under the PBS restriction very high risk patients (as defined by the GSLLD) can commence LLT at any cholesterol concentration.

IMPROVE-IT used a fixed dose of simvastatin (40 mg daily), which is considered a statin of medium intensity. During the IMPROVE-IT study, patients receiving 80 mg simvastatin had the dose reduced to 40 mg due to United States Food and Drug Administration (FDA) concerns regarding rhabdomyolysis at the higher dose. It is unknown whether this group would have had different outcomes. A dose of simvastatin 80 mg daily is considered high intensity; however, both of the market regulators in America and Australia, (FDA and Australian Therapeutic Goods Administration (TGA)) recommend this dose be reserved for patients at high risk of cardiovascular complications who have not achieved treatment goals on lower doses of simvastatin.

The reduction in LDL-C concentration between statins of differing doses and intensities is shown in Table 12. By comparison, ezetimibe (10 mg dose daily) produces an 18% reduction in baseline LDL-C concentration. Using the IMPROVE-IT approach of adding ezetimibe to a dose of 40 mg simvastatin, a similar reduction in LDL-C concentration could have been achieved by replacing the dual therapy with atorvastatin 80 mg or rosuvastatin 40 mg. All three approaches would have achieved an average LDL reduction from baseline of approximately 50-55%. In reducing elevated plasma LDL-C concentrations, all statins produce a non-linear dose response curve that reaches a plateau. More than 80% of the LDL-C lowering effect of a statin is achieved with 50% of the maximum dose.

The 2014 NICE Guidance Development Group consensus placed statins into three different intensity categories according to the percentage reduction in LDL-C concentration as shown in the following table.

**Table 12: Percentage reduction in LDL-C by statin dose (mg/day) and grouping of statins by intensity category used in the 2014 NICE Guidance**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Statin** | **Dose:****5 mg/day** | **Dose:****10 mg/day** | **Dose:****20 mg/day** | **Dose:****40 mg/day** | **Dose:****80 mg/day** |
| **fluvastatin** | - | - | 21%1 | 27%1 | 33%2 |
| **pravastatin** | - | 20%1 | 24%1 | 29%1 | - |
| **simvastatin** | - | 27%1 | 32%2 | 37%2 | 42%3,4 |
| **atorvastatin** | - | 37%2 | 43%3 | 49%3 | 55%3 |
| **rosuvastatin** | 38%2 | 43%3 | 48%3 | 53%3 | - |

Source Table 1, Appendix A; 2014 NICE Guidance/cg181. Reproduced from Review of Clinical Guidelines-CPHR Deakin University, p50.

120%-30%: low intensity

231%-40%: medium intensity

3Above 40%: high intensity

4Advice from Medicines and Healthcare products Regulatory Agency (MHRA): there is an increased risk of myopathy associated with high dose (80 mg simvastatin)

Established practice prior to the IMPROVE-IT study has been to use a statin first due to the greater volume of evidence available for statins that a reduction in LDL-C translates to reduced CV risk. A 1 mmol/L decrease in LDL-C by statin therapy reduces CV risk by approximately 22%. Results from IMPROVE-IT confirm that ezetimibe lowers the risk of CV events to an extent predicted by the relationship between absolute LDL reduction and CV risk obtained from previous studies with other lipid-lowering agents. These results confirm that reduction in LDL-C appears to be a valid surrogate for a reduction in rate of major vascular events as shown in Figure 3 below.

Figure 3: Plot of the IMPROVE-IT Trial Data and Statin Trials for Change in Low-Density Lipoprotein (LDL) Cholesterol versus Clinical Benefit.



Source: Cannon et al. (2015). Ezetimibe added to statin therapy after acute coronary syndromes. The New England Journal of Medicine, 372:2387-2397.

The risk reduction observed in the IMPROVE-IT trial was also consistent with the absolute reduction in LDL-C predicted by the Cholesterol Treatment Trialists’ Collaboration (CTTC) statin derived regression line. This supports the notion that LDL-C reduction by statins and ezetimibe confer similar benefits and that the real determinant of the relative risk reduction is the magnitude of the change in LDL-C rather than the mechanism by which the reduction is achieved[[62]](#endnote-63).

Whilst IMPROVE-IT is a secondary prevention study with a number of applicability issues to the Australian primary prevention population, and long-term patient outcomes may not be fully generalisable to the target population, it is none the less a significant trial with positive patient outcomes and predictable benefit. The trial showed a small, but statistically significant, 7.2% relative reduction in the risk of CV events (combined composite primary endpoint of coronary heart disease death, myocardial infarction and urgent coronary revascularization) in more than 18,000 patients with a recent coronary event, followed for seven years. This reduction in CV outcome was close to that predicted by the absolute reduction in LDL-C observed in the trial. The hazard ratio for clinical benefit per mmol of LDL-C reduction with ezetimibe in IMPROVE-IT was 0.80 (95% CI: 0.68-0.94), as compared with 0.78 (95% CI: 0.76-0.80) observed with statins in the CTTC meta-analysis[[63]](#endnote-64). However, the FDA expressed concern that this small effect would be further reduced in a primary prevention cohort[[64]](#endnote-65).

The Reference Group considered IMPROVE-IT supports the hypothesis that the magnitude of the reduction in LDL-C concentration is a valid surrogate outcome for a predictable decrease in CV risk for patients taking ezetimibe. In addition, there do not appear to be long-term safety issues for ezetimibe.

## 3.3 Economic evaluation of ezetimibe

In April 2016, the sponsor of ezetimibe submitted a modelled economic evaluation as part of its submission to the Review. The economic evaluation assessed the cost-effectiveness of adding ezetimibe to background treatment with a statin (simvastatin 40 mg) in the patient population eligible for PBS subsidised ezetimibe therapy. The economic evaluation consisted of a Markov model and the base case presented by MSD applied:

* Baseline Bettering the Evaluation and Care of Health (BEACH) Supplementary Analysis of Nominated Data (SAND) population patient characteristics.
* The change in TC:HDL ratios from the 2006 meta-analysis of ezetimibe add-on trials -19.5% vs -2.6% in the ezetimibe and comparator arms, respectively.
* Disutility value 0.055 for post-unstable angina and post MI.
* Time horizon=70 years.

This is the same Markov structure and transition probabilities as was previously considered by the PBAC in seven economic models for ezetimibe between December 2003 and March 2012.

The submission claimed that the reduction in CV events as observed in the IMPROVE-IT trial were consistent with the model presented previously to the PBAC. On this basis the submission presented an analysis of the cost-effectiveness of ezetimibe using the previous model.

Whilst the Review was not able to evaluate the model in the same manner as a submission to the PBAC, a preliminary review of the model by health economists and the Reference Group noted the following issues with the model:

* The submission stated that data from the IMPROVE-IT trial could be used to test the validity of the economic model used in previous PBAC submissions. Specifically, the submission considered that if the economic model accurately predicted the outcomes of the IMPROVE-IT trial, then it can reliably be used to assess the cost-effectiveness of ezetimibe in a broader patient population.
* The model did not reliably predict the number of CV events observed in the IMPROVE-IT trial based on the observed change in TC:HDL. The submission attributed the difference to a) the absence of the difference in the absolute rate of CHD events in the two arms in the first year of the IMPROVE-IT trial, explained by the recent acute coronary syndrome qualifying event necessary for inclusion into the trial; and b) the much higher risk of CHD events observed in the first year of the trial than was predicted by the MSD model. The submission claimed that if the numbers of events predicted by the model were multiplied by a factor of 3.98 for the first year and 1.11 for subsequent years (years 2-7) that the model predicted the number of observed events in the trial. The submission further claimed that as the calibration factors were the same for the statin and the ezetimibe plus statin arms of the economic model, that the model accurately predicts CV events in the future.

The Reference Group did not consider the approach used in the submission to be appropriate and noted the advice of the ESC that due to applicability issues, an economic model based on the results of IMPROVE-IT would not provide a reasonable estimate of the cost-effectiveness of the current use of ezetimibe on the PBS. The ESC advised a more appropriate method may be to create a model that uses evidence relevant to the PBS population and addresses the concerns raised previously by the PBAC.

Regarding the economic model presented in the sponsor’s submission, the Reference Group noted the results are particularly sensitive to:

* the efficacy estimates (changes in TC:HDL ratios for the intervention and comparator arms)
* the time horizon. The ICER using a 7 year time horizon (the duration of follow-up for the IMPROVE-IT trial) was $72,297 per QALY gained compared with $24,256 per QALY gained for a lifetime model (70 years). The substantial reduction in the ICER with the longer time horizon was considered by the Reference Group to highlight the uncertainty with the ICER associated with extrapolating results over a long period of time.

During the Review, alternative efficacy estimates were obtained for a sensitivity analysis from the meta-analysis of trials that enrolled primary, secondary or mixed prevention populations, all receiving second line treatment with ezetimibe plus statin (intervention) versus up-titrated statin (control). This *ad hoc* meta-analysis was conducted by Deakin for the Review. Using the result of this meta-analysis as input to the model (reduction in TC:HDL of -18.84% versus -9.65% in the ezetimibe and comparator arm, respectively) rather than the estimate used by the sponsor, the base case ICER based on a time horizon of 20 years almost doubled from $28,000 to $53,000/QALY (**Appendix J**, Tables 1.3 and 1.4, p 21).

Whilst the sponsor maintains that a lifetime horizon is appropriate, the Reference Group considered that a large proportion of patients using ezetimibe as second line therapy would be older than fifty years. The Reference Group acknowledged that 70 years may be an appropriate time horizon for the youngest participants in the model; however, the average age of the BEACH SAND population treated with PBS subsidised ezetimibe was over 60 years and selection of this time horizon did not seem plausible. The Reference Group requested a further analysis to explore the effect on the ICER of 10 year time horizon incremental extrapolations between 6 years and 70 years.

The results of this sensitivity analysis showed that the ICERs estimated as either a cost/LYG or cost/QALY remain unchanged when the time horizon extends beyond 30 years (**Appendix J**, p 20-21). This is because after the first 30 cycles (years) of the Markov model, the survival rate is zero and there is no difference in either the incremental costs or the outcomes.

The Reference Group also considered that from the results of the revised utilisation analysis, for the ‘red’, and a proportion of the ‘orange’ groups currently using ezetimibe, statins would be an appropriate comparator as maximally tolerated doses of statins/statins of higher potency are the therapies being replaced, not placebo.

The Reference Group agreed that for those patients using ezetimibe in accordance with the PBS restrictions, estimated at 46.9% (designated ‘green’ group from the revised utilisation analysis), placebo is the appropriate comparator.

Thus a weighted comparison with a proportion of use compared to up-titration of statin dose/switching to a higher potency statin and a proportion of use compared to placebo/non statin LLT, may be one way to estimate the cost-effectiveness of ezetimibe in current practice.

## 3.4 Key issues raised by stakeholders on TOR 3

Details of the submissions to the Review are provided in **Appendix H**.

### 3.4.1 Submissions to the Review

In the seven week public consultation held between 4 March and 22 April 2016 stakeholders raised the following key points in relation to TOR 3:

* If utilisation of ezetimibe is found to be consistent with the intent of the PBS within local clinical guidelines, it is unnecessary to review the cost-effectiveness of ezetimibe.
* There have been no other changes in the intervening period in terms of PBS listings, local treatment guidelines or choice of comparator that would warrant reconsideration of the cost-effectiveness of ezetimibe.
* New evidence from the IMPROVE-IT study has confirmed the benefit of adding ezetimibe to statins.
* Ezetimibe achieved a reduction in LDL-C of 0.4 mmol/L compared with placebo in the IMPROVE-IT trial.
* The IMPROVE-IT result has been described as proof that LDL-C is a causal factor of CVD and reducing LDL-C reduces CVD.

### 3.4.2 Outcomes from the stakeholder forum

The Reference Group sought any further recent evidence that may inform its consideration of TOR 3. Participants agreed to identify other relevant studies to the Review Secretariat. Following the stakeholder forum the sponsor provided the citations.

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 study, and also addresses questions in relation to the safety of ezetimibe.
* The experiences of failed studies (studies that did not demonstrate outcomes) is also relevant to this Review.

The [Stakeholder Forum Outcome Statement](http://www.pbs.gov.au/reviews/ezetimibe-review-files/ezetimibe-stakeholder-forum-outcomes-report.pdf) is available on the Review website and at **Appendix F**. Stakeholder responses to the Stakeholder Forum Outcome Statement are available on the Review’s [Public Consultation website](http://www.pbs.gov.au/info/reviews/ezetimibe-review-public-consultation).

### 3.4.3 Stakeholder submissions to the draft Report

Stakeholders raised the following points in their responses to the draft Report provided on the PMR website from 30 January to 10 February 2017.

* Stakeholders highlighted an important new article by J G Robinson et al in the Journal of American College of Cardiology, December 2016.
* Overall, stakeholders considered that all clinical evidence supported ezetimibe as a second line therapeutic option to lower LDL-C and other harmful lipids in patients at increased risk of CV events.
* Key findings of the IMPROVE-IT study were stated to be:
	+ validation of LDL-C as a surrogate
	+ the benefit of addition of ezetimibe has been shown in a high risk (secondary prevention) population so that the issue of applicability to the PBS population with a low risk of CV disease remains without adequate evidence in terms of the extent of benefit from adding ezetimibe
	+ there was no gain in mortality in populations with high risk of CV events.
* Additional clinical comments from stakeholders were:
	+ The response of patients to ezetimibe has been found to be subject to high levels of individual variation, possibly associated with pharmacodynamic factors.
	+ One submission commented on the apparently high doses of ezetimibe in the marketed product when the ED50 (median effective dose i.e. dose for 50% of the population to have the specified effect) has never been shown to reduce mortality. *The Review notes that this is a regulatory issue and out of scope of this Review*.
	+ The future availability of PCSK 9 inhibitors will provide a major stimulus to effective treatments to reduce CV events.
* A 2016 New England Journal of Medicine data report from the Framingham study reported that maintaining low blood pressure and LDL-C decreased the risk of developing dementia.
* Cost-effectiveness of ezetimibe:
	+ One submission considered that the evidence presented did not provide a basis for a review of cost-effectiveness.
	+ Three submissions were concerned about the addition of a second comparator in considering cost-effectiveness of ezetimibe in this Review. The second comparator, higher doses of statin, was felt to be inconsistent with the position of ezetimibe as a second line agent. These submissions noted that the PBAC did not considered higher dose statins as a comparator when considering ezetimibe for listing on the PBS.
	+ The main concern about the model was in regard to the duration of the model. Submissions were concerned that a lifetime duration was consistent with the current statements for chronic diseases in the *Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee*.
* Additional commercial-in-confidence technical comments on the model in the MSD submission were provided to ESC and DUSC.

# List of Appendices

## Appendix A – History of PBS listings

## Appendix B – PBS ezetimibe restrictions

## Appendix C – Key dates

## Appendix D – Reference Group membership

## Appendix E – Analysis of Utilisation Data

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## Appendix G – Review of clinical guidelines

## Appendix H – Public consultation

## Appendix I – Systematic Literature Review

## Appendix J – Modelled Economic Evaluations

**(NOT FOR PUBLICATION-contains commercial-in-confidence information)**

# References

1. Thomson PD What to Believe and do about Statin Associated Adverse Effects *JAMA* November 15, 2016 Volume 316, Number 19. [↑](#endnote-ref-2)
2. Cannon CP, Blazing MA, Giugliano RP et al Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes *N Engl J Med* 2015; 372:2387-2397 [June 18, 2015](http://www.nejm.org/toc/nejm/372/25/) DOI: 10.1056/NEJMoa1410489. [↑](#endnote-ref-3)
3. Eisen A, Cannon CP, Blazing MA et al The Benefit of Adding Ezetimibe to Stain Therapy in Patients with Prior Coronary Artery Bypass Graft Surgery and Acute Coronary Syndrome in the IMPROVE-IT Trial. *European Heart J* (2016)37, 3576-3584. [↑](#endnote-ref-4)
4. Jacoby DS, Rader DJ. Improving Cardiovascular Outcomes by Intensifying Low Density Lipoprotein Lowering Therapy in High Risk Patients *European Heart J* (2016)37, 3576–3584. [↑](#endnote-ref-5)
5. Bohula et al :Atherothrombotic Risk Stratification and Ezetimibe for Secondary Prevention *JACC* Vol.69,No.8 2017. [↑](#endnote-ref-6)
6. Department of Health, (2016). Pharmaceutical Benefits Scheme (PBS) [GENERAL STATEMENT FOR LIPID-LOWERING DRUGS PRESCRIBED AS PHARMACEUTICAL BENEFITS](http://www.pbs.gov.au/info/healthpro/explanatory-notes/gs-lipid-lowering-drugs). [online] Accessed 9 Dec. 2016. [↑](#endnote-ref-7)
7. Cannon CP, Blazing MA, Giugliano RP et al Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes *N Engl J Med* 2015; 372:2387-2397 June 18, 2015DOI: 10.1056/NEJMoa1410489. [↑](#endnote-ref-8)
8. Bohula et al: Atherothrombotic Risk Stratification and Ezetimibe for Secondary Prevention *JACC* Vol.69,No.8 2017. [↑](#endnote-ref-9)
9. Eisen A, Cannon CP, Blazing MA et al The Benefit of Adding Ezetimibe to Stain Therapy in Patients with Prior Coronary Artery Bypass Graft Surgery and Acute Coronary Syndrome in the IMPROVE-IT Trial. *European Heart J* (2016) 37,3576-3584. [↑](#endnote-ref-10)
10. Jacoby DS, Rader DJ. Improving Cardiovascular Outcomes by Intensifying Low Density Lipoprotein Lowering Therapy in High Risk Patients *European Heart J* (2016)37, 35856-3587. [↑](#endnote-ref-11)
11. Yang YJ, See SH, Kim BS, Cho YK et al. Combination Therapy of Rosuvastatin and Ezetimibe in Patients with High Cardiovascular Risk. *Clin Ther.*2016;38:107-117. [↑](#endnote-ref-12)
12. [Australian Commission on Safety and Quality in Healthcare](https://www.safetyandquality.gov.au/) [↑](#endnote-ref-13)
13. Department of Health, (2016). [online] [PBAC Guidelines for preparing submissions version 5.0](https://pbac.pbs.gov.au/). Accessed 1 Nov. 2016. [↑](#endnote-ref-14)
14. Department of Health, (2016). [online] [Post-market reviews](http://www.pbs.gov.au/info/reviews/subsidised-medicines-reviews). Accessed 1 Nov. 2016. [↑](#endnote-ref-15)
15. Department of Health. (2016). [Pharmaceutical Benefits Scheme (PBS) Home](http://www.pbs.gov.au/). [online] Accessed 1 Nov. 2016. [↑](#endnote-ref-16)
16. Anon, (2016). [online] [Post-market Review Framework 2015](http://www.pbs.gov.au/info/reviews/subsidised-medicines-reviews). Accessed 1 Nov. 2016. [↑](#endnote-ref-17)
17. Therapeutic Goods Administration, [Product Information Ezetrol (Ezetimibe)](https://www.tga.gov.au/sites/default/files/auspar-ezetimibe-130228-pi.doc), (2016). Accessed 9 Dec. 2016. [↑](#endnote-ref-18)
18. Australian Institute of Health and Welfare, 2011, Cardiovascular Disease Australian Facts 2011. [↑](#endnote-ref-19)
19. Australian Bureau of Statistics, 2015, [3303.0 – Causes of Death, Australia, 2013](http://www.abs.gov.au/ausstats/abs%40.nsf/Lookup/by%20Subject/3303.0~2013~Main%20Features~Leading%20Causes%20of%20Death~10001). [↑](#endnote-ref-20)
20. Australian Institute of Health and Welfare, 2015, [Burden of Disease](http://www.aihw.gov.au/burden-of-disease/). [↑](#endnote-ref-21)
21. eTG Complete, (2016). [online] [Cardiovascular Disease Risk Stratification](https://tgldcdp.tg.org.au/viewTopic?topicfile=cardiovascular-disease-risk-stratification#toc_d1e182). Accessed 25 Nov 2016. [↑](#endnote-ref-22)
22. eTG Complete , (2016). [online] [Dyslipidaemia](https://tgldcdp.tg.org.au/viewTopic?topicfile=dyslipidaemia#toc_d1e47). Accessed 25 Nov. 2016. [↑](#endnote-ref-23)
23. eTG Complete , (2016). [online] .[Dyslipidaemia](https://tgldcdp.tg.org.au/viewTopic?topicfile=dyslipidaemia#cvg-c07-s6). Accessed 25 Nov. 2016. [↑](#endnote-ref-24)
24. National Vascular Disease Prevention Alliance, (2016). [online] [Absolute cardiovascular risk calculator](http://www.cvdcheck.org.au/). Accessed 1 Nov. 2016. [↑](#endnote-ref-25)
25. Stone NJ et al (2013) ACC/AHA Guideline on the Treatment of Blood cholesterol to Reduce Atherosclerotic Cardiovascular Risk In Adults A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, Circulation, 129 [Suppl 2]:S1-S45. [↑](#endnote-ref-26)
26. Thomson PD What to Believe and do about Statin Associated Adverse Effects *JAMA* November 15, 2016 Volume 316, Number 19. [↑](#endnote-ref-27)
27. Chowdhury R, Khan H, Heydon E et al. Adherence to Cardiovascular Therapy: a meta-analysis of prevalence and clinical consequences. *Eur Heart J* 2013;34:2940-8. [↑](#endnote-ref-28)
28. Doust J, Sanders S, Shaw J, Glasziou P. Prioritising CVD prevention therapy - absolute risk versus individual risk factors. *Aust Fam Physician* 2012; 41:805-809. [↑](#endnote-ref-29)
29. Bohula et al: Atherothrombotic Risk Stratification and Ezetimibe for Secondary Prevention *JACC* Vol.69,No.8 2017. [↑](#endnote-ref-30)
30. Anderson T.J., G.B. Mancini et al. The New Dyslipidemia Guidelines: What Is the Debate? *Canadian Journal of Cardiology* (2015) 31:605-612. [↑](#endnote-ref-31)
31. Morris P, Ballantyne C M et al. Review of Clinical Practice Guidelines for the Management of LDL-Related Risk. *J Am Coll Cardiol*. 2014;64(2):196-206. [↑](#endnote-ref-32)
32. McKenney JM. Something important is missing in the ACC/AHA cholesterol treatment guidelines. *J Am Pharm Assoc*. 2015;55(3):324-329. [↑](#endnote-ref-33)
33. Nayor M., Vasan R.S., Recent Update to the US Cholesterol Treatment Guidelines. A Comparison with International Guidelines. *Circulation.* 2016;133:1795-1806. [↑](#endnote-ref-34)
34. Waite LH, Phan YL, Spinler SA. What's next for dyslipidemia management? The 2013 ACC/AHA Guidelines, the NLA recommendations, and beyond. Journal of the American Pharmacists Association (2016) 56:284-292. [↑](#endnote-ref-35)
35. Bohula et al: Atherothrombotic Risk Stratification and Ezetimibe for Secondary Prevention *JACC* Vol.69,No.8 2017. [↑](#endnote-ref-36)
36. Eisen A, Cannon CP, Blazing MA et al The Benefit of Adding Ezetimibe to Stain Therapy in Patients with Prior Coronary Artery Bypass Graft Surgery and Acute Coronary Syndrome in the IMPROVE-IT Trial. *European Heart J* (2016) 37,3576-3584. [↑](#endnote-ref-37)
37. Jacoby DS, Rader DJ. Improving Cardiovascular Outcomes by Intensifying Low Density Lipoprotein Lowering Therapy in High Risk Patients *European Heart J* (2016)37, 35856-3587. [↑](#endnote-ref-38)
38. Yang YJ, See SH, Kim BS, Cho YK et al. Combination Therapy of Rosuvastatin and Ezetimibe in Patients with High Cardiovascular Risk. *Clin Ther.*2016;38:107-117. [↑](#endnote-ref-39)
39. Doust J, Sanders S, Shaw J, Glasziou P. Prioritising CVD prevention therapy - absolute risk versus individual risk factors. *Aust Fam Physician* 2012; 41:805-809. [↑](#endnote-ref-40)
40. Barr ELM et al, (2005). [AusDiab 2005: The Australian Dibetes, Obseity and Lifestyle Study](https://www.baker.edu.au/Assets/Files/AUSDIAB_Report_2005.pdf). [↑](#endnote-ref-41)
41. Doust J, Sanders S, Shaw J, Glasziou P. Prioritising CVD prevention therapy - absolute risk versus individual risk factors. *Aust Fam Physician* 2012; 41:805-809. [↑](#endnote-ref-42)
42. Silverman, M.G., Ference, B.A., Im, K., Wiviott, S.D., Giugliano, R.P., Grundy, S.M., Braunwald, E. and Sabatine, M.S., 2016. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA* *316*(12), pp.1289-1297. [↑](#endnote-ref-43)
43. Silverman, M.G., Ference, B.A., Im, K., Wiviott, S.D., Giugliano, R.P., Grundy, S.M., Braunwald, E. and Sabatine, M.S., 2016. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA* *316*(12), pp.1289-1297. [↑](#endnote-ref-44)
44. Thomson PD What to Believe and do about Statin Associated Adverse Effects *JAMA* November 15, 2016 Volume 316, Number 19. [↑](#endnote-ref-45)
45. Thomson PD et al Statin Associated Side Effects. *J Am Coll Cardiol*.2016;67(20):2395-2410. [↑](#endnote-ref-46)
46. Cohen JD, Brinton EA, ITO MK et al. Understanding Satin Use in America and Gaps in Patient Education (USAGE): an internet based survey of 10,138 current and former statin users. *J Clin Lipidol* 2012;6:208-15. [↑](#endnote-ref-47)
47. OECD (2015), [Health at a Glance 2015: How does Australia compare?](https://www.oecd.org/australia/Health-at-a-Glance-2015-Key-Findings-AUSTRALIA.pdf). [↑](#endnote-ref-48)
48. National Vascular Disease Prevention Alliance (2012). [Australian Absolute Cardiovascular Disease Risk Calculator](http://www.cvdcheck.org.au/). [↑](#endnote-ref-49)
49. Cannon CP, Blazing MA, Giugliano RP et al Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes *N Engl J Med* 2015; 372:2387-2397 June 18, 2015DOI: 10.1056/NEJMoa1410489. [↑](#endnote-ref-50)
50. Pandor, A. Ara, R. M. et al Ezetimibe monotherapy for cholesterol lowering in 2,722 people: systematic review and meta-analysis of randomized controlled trials *Journal of Internal Medicine*, 2009, 265(5)568-80. [↑](#endnote-ref-51)
51. Bohula et al :Atherothrombotic Risk Stratification and Ezetimibe for Secondary Prevention *JACC* Vol.69,No.8 2017. [↑](#endnote-ref-52)
52. Ray, K.K., Ginsberg, H.N., Davidson, M.H., Pordy, R., Bessac, L., Minini, P., Eckel, R.H. and Cannon, C.P., 2016. Reductions in Atherogenic Lipids and Major Cardiovascular Events: A Pooled Analysis of 10 ODYSSEY Trials Comparing Alirocumab to Control. *Circulation*, 2016 Oct 24. [↑](#endnote-ref-53)
53. Silverman, M.G., Ference, B.A., IM, K., Wiviott, S.D., Giugliano, R.P., Grundy, S.M., Braunwald, E. and Sabatine, M.S., 2016. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA* *316*(12), pp.1289-1297. [↑](#endnote-ref-54)
54. Anderson TJ (2016) Editorial: Bringing Structure to the Art of Lipid Lowering Therapy. *Journal of the American College of Cardiology* Vol68,No.22. [↑](#endnote-ref-55)
55. Robinson JG (2016) Determining When to Add Non-Statin Therapy - A Quantitative Approach. *Journal of the American College of Cardiology*, Vol68,No.22. [↑](#endnote-ref-56)
56. Bohula et al: Atherothrombotic Risk Stratification and Ezetimibe for Secondary Prevention *JACC* Vol.69,No.8 2017. [↑](#endnote-ref-57)
57. AHRQ 2009. Sharma M, Ansari MT, Abou-Setta AM, Soares-Weiser K, Ooi TC, Sears M, et al. Systematic review: comparative effectiveness and harms of combination therapy and monotherapy for dyslipidemia. Ann Intern Med. 2009a;151:622-30. [↑](#endnote-ref-58)
58. Mikhailidis DP Comparative efficacy of the addition of ezetimibe to statin vs statin titration in patients with hypercholesterolaemia: systematic review and meta-analysis. *Curr Med Res Opin.* 2011 Jun;27(6):1191-210. [↑](#endnote-ref-59)
59. Ara R, Tumur I, Pandor A, Duenas A, Williams R, Wilkinson A, et al. Ezetimibe for the treatment of hyper cholesterolaemia: a systematic review and economic evaluation. *Health Technology Assessment* 2008;12(21) [↑](#endnote-ref-60)
60. NICE (2015). [Final appraisal determination: Ezetimibe for treating primary heterozygous famial and non-famial hypercholesterolaemia](https://www.nice.org.uk/guidance/TA385/documents/final-appraisal-determination-document). [↑](#endnote-ref-61)
61. Cannon CP, Blazing MA, Giugliano RP et al Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes *N Engl J Med* 2015; 372:2387-2397 [June 18, 2015](http://www.nejm.org/toc/nejm/372/25/) DOI: 10.1056/NEJMoa1410489. [↑](#endnote-ref-62)
62. Ray, K.K., Ginsberg, H.N., Davidson, M.H., Pordy, R., Bessac, L., Minini, P., Eckel, R.H. and Cannon, C.P., 2016. Reductions in Atherogenic Lipids and Major Cardiovascular Events: A Pooled Analysis of 10 ODYSSEY Trials Comparing Alirocumab to Control. *Circulation*, 2016 Oct 24. [↑](#endnote-ref-63)
63. Cannon CP, Blazing MA, Giugliano RP et al Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes *N Engl J Med* 2015; 372:2387-2397 June 18, 2015DOI: 10.1056/NEJMoa1410489. [↑](#endnote-ref-64)
64. Huston L, (2016). [online] [CardioBrief: FDA Panel Rejects Broader Ezetimibe Indication](http://www.medpagetoday.com/ClinicalFocus/LDLCholesterol/56328?xid=nl_mpt_ACC_confreporter_20160825&), Medpage Today Accessed 8 Dec. 2016. [↑](#endnote-ref-65)