Submission to

THE REVIEW SECRETARIAT

in support of

EZETROL (ezetimibe MSD-SP LIMITED) **AND** VYTORIN (ezetimibe/simvastatin)

for

Post Market Ezetimibe Review

April 2016

MSD

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EXECUTIVE SUMMARY

MSD welcomes the opportunity to contribute to the ezetimibe review. Ezetimibe is a cholesterol-lowering therapy used to treat cardiovascular disease (CVD), a top cause of death in Australia. High cholesterol contributes a third CVD's disease burden1. Less than half of patients with high cholesterol take medicines for their condition2, of which only a third reach recommended cholesterol targets3.

Ezetimibe has a different mechanism of action to statins & other cholesterol lowering drugs: it inhibits absorption of cholesterol in the gut4. It was listed on the PBS in 2004 & can be used in patients not at target, as monotherapy for those with contraindications or intolerance to statins, and in combination with statins for those who are uncontrolled despite treatment with maximally-tolerated statin doses.

1 in 10 Australians have a precaution against statins5 so there is a high need for treatments beyond 1st-line statin therapy. 278,000 Australians take ezetimibe alone or in combination with statins.

This submission shows that ezetimibe is a cost effective therapy, used within PBS restrictions, consistent with best-practice clinical guidelines:

Ezetimibe reduces CV events and is cost-effective when used in <u>combination with statins</u> - in the IMPROVE-IT trial, the reduction in CV events relative to cholesterol lowering with ezetimibe, was consistent to that seen in outcomes studies of other cholesterol lowering drugs. An analysis presented here applies the IMPROVE-IT results to the same model used to demonstrate ezetimibe's cost-effectiveness in previous submissions and confirms the current cost-effectiveness of ezetimibe when used <u>in combination with statins</u>. The model delivers base-case ICER of $24,256 per life year gained and estimates that ezetimibe has saved 2,785 Australian lives over the past 6 years.

Ezetimibe shows better cost-effectiveness as <u>monotherapy</u> than previously provided for – ezetimibe's cost-effectiveness in monotherapy patients has improved due to a 29% increase in the cost of its monotherapy comparator, cholestyramine.

It is used within PBS restrictions – a longitudinal analysis of patient transitions between different cholesterol lowering medicines was conducted using a PBS data sample. This assessed patient transitions between therapies against ezetimibe restrictions, and found that PBS eligibility criteria for ezetimibe were adhered to in 9 out of 10 patients. In the remaining patients, transitions could be explained by clinically justifiable treatment changes or were due to limitations of the data / analyses.

The current PBS restrictions for ezetimibe are consistent with best practice clinical guidelines - local NVDPA, NHF and RACGP guidelines were assessed together with a recent American College of Cardiology consensus statement. These restrict ezetimibe use to circumstances where patients are not at target following use of maximally tolerated doses of a statin.

Ezetimibe's cost effectiveness will be further enhanced when it loses patent exclusivity in mid-2018.

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

[2] Heart Foundation. Heartwatchsurvey 2011.

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

[4] EZETROL (ezetimibe). Australian Approved Product Information. Sydney: MSD. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-05310-3&d=20151030161146224 12

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

OVERVIEW OF EZETIMIBE REIMBURSEMENT

Ezetimibe was first listed on the PBS in 2004, following a positive recommendation by the Pharmaceutical Benefits Advisory Committee (PBAC) in 2003. Since its listing, the PBAC has considered numerous submissions, intended to align the PBS restrictions with evolving clinical practice and/or guidelines, and to ensure equitable access for high-risk patients.

The PBS restrictions presented in Section A.2.3 are a result of these multiple considerations. They reflect two discrete uses of ezetimibe – as monotherapy for patients not at target and with contraindications or intolerance to statins, and in combination with statins for patients not at target despite treatment with maximally-tolerated statin doses (**Table 1** The agreed price of ezetimibe in these two populations is different, with the PBS list price being weighted equally as use in the two populations was expected to be similar. This ex-manufacturer price has remained constant until April 2016 whereupon ezetimibe was subject to a 5% statutory reduction.

Table 1: Overview of PBAC considerations of ezetimibe use

	Monotherapy	Combination with statin
Populations	Intolerance or contraindications to statin Homozygous sitosterolemia	HoFH, CHD, diabetes, PVD, HeFH, hypertension, family history of CHD, high dose statin intolerant
PBAC consideration	Jun-03, Sep-03, Nov-06	Jun-03, Dec-03, Nov-05, Nov-06
Main comparator	Cholestyramine	Placebo
Clinical claim	Non-inferior, therapeutic relativity agreed by the PBAC is ezetimibe 10 mg daily equal to cholestyramine 17.2 g daily	Superior on the basis of reduction in lipid levels
Economic analysis	Cost-minimisation analysis	Cost utility analysis - modelled economic evaluation transformed lipid levels to final patient outcomes of interest
ICER	N/A	$23,996 to $42,000 per LYG[1]
Ex-man price[2] (weight)	[redacted]	
Final ex-man price		

Abbreviations: HeFH=heterozygous familial hypercholesterolaemia, HoFH=homozygous familial hypercholesterolaemia, LDL=low density lipoprotein. CHD=coronary heart disease, PVD=peripheral vascular disease, LYG = life year gained, ICER = incremental cost effectiveness ratio.

1. Initial listing was made on the basis of an incremental cost per LYG of $23,996. Subsequent extensions to the listing were in populations at lower overall risk of events resulting in higher ICERs (range $27,000 to $42,000 per LYG). In making its recommendation, the Committee accepted that ezetimibe was cost effective.
2. AEMP quoted is current one following 5% cut on 1st April 2016. Original approved prices were $[redacted]/pack (mono) and $[redacted]/pack (combination).

Of relevance to this review was the 2010 submission requesting an amendment to the definition of 'inadequate control with a statin' in the restriction wording for ezetimibe. Historically, the restriction nominated specific doses of statins that needed to be administered before a patient could qualify for ezetimibe add-on treatment. The submission requested a change to the wording, to recognise the categorisation of high potency statins. When approving this application in November 2010, the PBAC requested wording that did not specify a particular dose of a statin; rather, the wording should stipulate a three month trial with the maximum tolerated dose of a statin.

In making this decision, the Committee noted that this option "*allowed ezetimibe to be added as clinically appropriate while continuing to support uptitration of statins as the first line treatment of hypercholesterolaemia*" and that "*such a change was also consistent with clinical practice and quality use of medicine*."[6]

Context for this post-market review

In November 2013, the PBAC expressed concern that the listing of ezetimibe with statin co-packs and combination products on the PBS may direct use away from optimal dose titration of statins. The

[6] http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2010-11/pbac-psd-ezetimibe-nov10

PBAC also noted that in contrast to statins, there was, at the time, no long term patient relevant outcome data for ezetimibe, and that PBS expenditure on the drug was high. Following the release of the results of the ezetimibe IMPROVE-IT outcomes trial, the PBAC expressed concern this may increase utilisation (away from statin up-titration).

On 14 August 2015, the PBAC recommended a post-market review of ezetimibe. Following public consultation and consideration by the PBAC in December 2015, the Minister for Health approved the final Terms of Reference (TOR) for the Review:

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.

Overview of submission

This submission is being made to address the individual TOR as follows (see Table 2).

Table 2: How terms of reference are addressed in the submission

Term of reference		Purpose	Results	How used in submission
1	Utilisation	Review utilisation patterns (Section E)	Growth is as expected. Utilisation is in line with restrictions	Supports clinical management algorithm (Section A.5)
2	Clinical guidelines	Review clinical guidelines	Guidelines are aligned to PBS restrictions	PBS restrictions (Section A.2.3) are appropriate
		Compare guidelines to eze utilisation	Eze use is consistent with guidelines / PBS restrictions	
		Justification of main comparator	Eze add-on therapy – placebo is the main comparator	Present an updated literature search and economic analysis as part of TOR 3 (see below)
			Eze mono – cholestyramine is the main comparator	
3	Clinical studies	Literature search to compare ezetimibe to comparator in specific setting, focussing on studies reporting patient outcomes	Eze add-on therapy – IMPROVE-IT study identified	Supports superiority conclusions over placebo (Section B.(i))
				Supports use of changes in lipid profile to estimate cost effectiveness (Section B.8 and Section C (i))
			Ezetimibe monotherapy – updated clinical comparison	Supports non-inferiority conclusions over cholestyramine (Section B (ii))
	Cost effect-iveness	Use IMPROVE-IT data to validate economic model	Model shown to be robust and reliable	Model can be used to re-assess cost effectiveness of eze add-on treatment
		Re-assess CE of eze add-on using model	Base case of $[redacted]/LYG is consistent with past decisions	Justifies no change to ezetimibe add-on price of $[redacted]/pack (ex-man)
		Update cost-minimsation analysis of eze mono	Cost of comparator has increased by around 29%	Justifies increase in price for eze mono to $[redacted]/pack (ex-man)
		Review weighting of eze add-on relative to ezetimibe monotherapy	Ezetimibe use is 26.5% as monotherapy and 73.5% as add-on therapy	Justifies an increase in weighted price from $[redacted]/pack to $[redacted]/pack (ex-man)

Abbreviations: eze = ezetimibe, mono = monotherapy, LYG = life year gained, CE = cost effectiveness

The review of cost effectiveness requested in TOR 3 supports an 11% increase in the price of ezetimibe. Despite this, MSD is requesting that the current AEMP of $[redacted]/pack be maintained. This should provide confidence to the PBAC that the use of ezetimibe continues to be cost effective.

TOR 1: REVIEW OF EZETIMIBE UTILISATION

Purpose of TOR 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.

Approach: analysis of ezetimibe utilisation (single tablet and FDCs / co-packs) in the context of use of lipid therapies; longitudinal analyses to inform utilization and clinical place in therapy of ezetimibe.

Results: growth in ezetimibe costs (i.e. excluding cost of statin component) have peaked in 2013/2014 and have stabilised since then to a 4% rate of growth for the current financial year; growth in PBS script volume has followed a similar trend; in contrast, PBS outlays for ezetimibe containing presentations in the current financial year are expected to be in negative growth (around -14%), due to the cumulative impact of a number of pricing events that occurred recently.

An analysis of patient numbers highlights the important role of ezetimibe in the management of hypercholesterolaemia in Australia, with around 256,000 patients expected to be treated in 2015/2016. Across the last five financial years, average annual growth in patient numbers was around 9%. This reflects the increasing burden of hypercholesterolaemia, and an appreciation by clinicians of the role of 2nd line agents in treating patients not at target despite maximally tolerated doses of statins.

The longitudinal data presented in the submission allows us to conclude that in 9 of 10 patients, PBS eligibility criteria for ezetimibe were adhered to. In most of the remaining patients, the transitions are inconclusive as they could be an artefact of the limitations of the data / analyses, or may be the result of treatment changes based on the physician's assessment of patient needs and clinical judgment.

Conclusions: whilst use of ezetimibe is growing, it remains consistent with the PBS eligibility criteria. Therefore, it can be concluded that the growth reflects increased use of an effective, second line lipid lowering therapy. Recent price reductions, including the April 2016 5% statutory cut, have attenuated the modest historic growth in total PBS expenditure on ezetimibe.

Ezetimibe was first listed on the PBS in August 2004 and various fixed dose combinations (FDC's) or co-packs with simvastatin, atorvastatin and rosuvastatin have since been reimbursed. Its use can be described in two discrete populations, and is analysed in the following sections:

- As an add-on treatment, in patients not at target despite maximum tolerated dose of a statin
- As monotherapy for patients in whom treatment with a statin is contraindicated or not tolerated

Overview of utilisation

Utilisation of ezetimibe is described using publicly available PBS script and benefit paid statistics[7] and a 10% PBS concessional cohort sample (from Model Solutions). These data sources are appropriate because they provide the most accurate and up to date representation of ezetimibe utilisation. The concessional cohort was chosen because most statin script items are now below the general co-payment level and the majority of statin and ezetimibe users are concessional patients.

The total PBS cost of ezetimibe-containing presentations is presented in **Error! Reference source not found.** and that of the ezetimibe component of these (i.e. excluding the statin component) in **Error! Reference source not found.**. Total scripts for ezetimibe and combinations are presented in Table 3 below.[8]

Table 3: Total cost of ezetimibe and combinations to PBS ($m)

[7] http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp

[8] Data presented for the current 2015/2016 financial year represent actuals from July 2015 to January 2016, pro-rata for the full financial year including taking into account the 5% statutory price cut affecting ezetimibe (and combination items) from 1st April 2016

	2010/2011	2011/2012	2012/2013	2013/2014	2014/2015	2015/2016
EZETROL®	$58.8	$63.1	$67.9	$75.1	$75.8	$70.7
VYTORIN®	$73.2	$81.4	$89.2	$100.5	$94.6	$61.6
ATOZET®	$0.0	$0.0	$0.0	$1.0	$8.7	$13.7
ROSUZET®	$0.0	$0.0	$0.0	$0.0	$1.2	$9.4
Cost to PBS	$132.0	$144.5	$157.1	$176.6	$180.3	$155.4
Growth (%)		9.5%	8.7%	12.4%	2.1%	-13.8%

Table 4: Cost of ezetimibe and combinations to PBS – ezetimibe component ($m)

	2010/2011	2011/2012	2012/2013	2013/2014	2014/2015	2015/2016
EZETROL®	$58.8	$63.1	$67.9	$75.1	$75.8	$70.7
VYTORIN®	$42.6	$47.6	$52.5	$59.5	$60.6	$58.2
ATOZET®	$0.0	$0.0	$0.0	$0.8	$7.3	$12.8
ROSUZET®	$0.0	$0.0	$0.0	$0.0	$1.1	$8.9
Cost to PBS	$101.4	$110.7	$120.4	$135.3	$144.7	$150.6
Growth (%)		9.2%	8.7%	12.3%	7.0%	4.1%

Note: Refer to calculations in Section E.1.

Table 5: Total scripts of ezetimibe and combinations

	2010/2011	2011/2012	2012/2013	2013/2014	2014/2015	2015/2016
EZETROL®	980,784	1,058,820	1,143,997	1,269,831	1,281,912	1,234,953
VYTORIN®	710,434	798,517	884,849	1,005,492	1,024,666	1,015,635
ATOZET®	0	0	0	12,875	124,001	223,764
ROSUZET®	0	0	0	0	18,577	155,679
Total Scripts	1,691,218	1,857,337	2,028,846	2,288,198	2,449,156	2,630,031
Growth (%)		9.8%	9.2%	12.8%	7.0%	7.4%

Growth in ezetimibe costs (i.e. excluding cost of statin component) have peaked in 2013/2014 and have since stabilised to a 4% rate of growth for the current financial year. Growth in PBS script volume has followed a similar trend. In contrast, PBS outlays for ezetimibe containing presentations in the current financial year are expected to be in negative growth (around -14%) due to the cumulative impact of a number of pricing events that occurred recently.

An analysis of patient numbers (Error! Reference source not found.) highlights the important role of ezetimibe in managing hypercholesterolaemia, with 278,000 patients expected to be treated this financial year. Whilst there are more than a quarter of a million patients on ezetimibe, this only represents approximately 10% of total patients on lipid lowering therapy (Error! Reference source not found.).

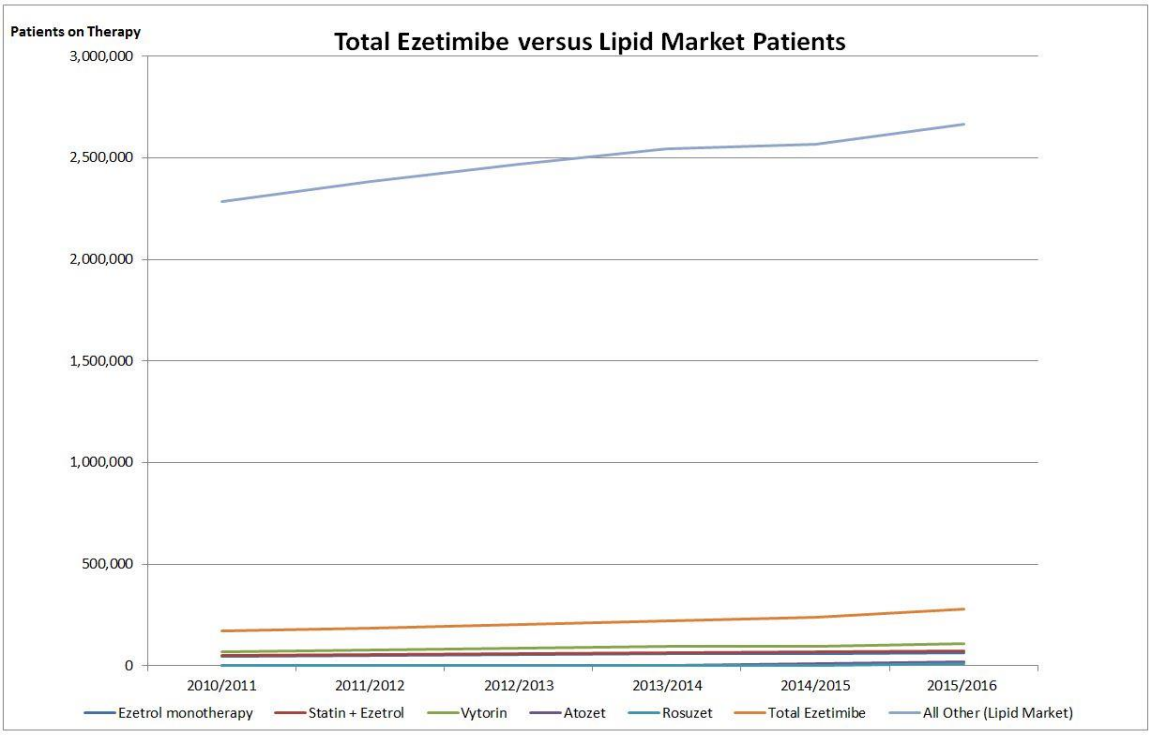
Whilst ezetimibe patient growth is higher than that of the lipid market, this is not surprising given: (1) patient numbers have increased off a much lower baseline; (2) the greater awareness of clinicians on the importance to manage cardiovascular risk; (3) the favourable safety and tolerability profile of ezetimibe in comparison to other non-statin lipid lowering agents which could result in better medication adherence and compliance; (4) the increased availability of co-pack and FDC formulations which increases clinicians' motivation to prescribe a second agent and improves adherence and compliance by reducing cost of treatment and pill burden.

Table 6: Average number of patients on ezetimibe and combinations versus total lipid market

	2010/2011	2011/2012	2012/2013	2013/2014	2014/2015	2015/2016
EZETROL monotherapy	47,833	51,064	55,769	59,253	61,562	63,961
EZETROL + statin	52,826	56,419	60,824	65,577	67,709	60,575
VYTORIN	69,332	77,990	87,543	94,548	97,804	96,942
ATOZET	0	0	0	1,501	11,640	21,005
ROSUZET	0	0	0	0	1,607	13,467
Total ezetimibe	169,991	185,472	204,136	220,878	240,322	255,949
Ezetimibe patient growth		9.1%	10.1%	8.2%	8.8%	6.5%
Lipid market excluding Ezetimibe	2,287,193	2,385,572	2,469,278	2,543,175	2,566,396	2,665,126
Lipid Market Growth		4.3%	3.5%	3.0%	0.9%	3.8%
Ezetimibe Patients vs Total Lipid Market	7.4%	7.8%	8.3%	8.7%	9.4%	9.6%

Note: The data is sourced from the 10% concessional PBS sample from Model Solutions whilst 2015/2016 numbers have been extrapolated using a linear trend.

Figure 0-1: Patients on ezetimibe monotherapy, ezetimibe combinations and other lipid therapies



Analysis of utilisation patterns

Section E.2 describes utilisation patterns for patients treated with ezetimibe presentations via an analysis of longitudinal PBS data. The intent is to understand whether the use described previously is consistent with PBS restrictions and clinical guidelines.

Utilisation patterns were assessed and categorised into 7 distinct groups on the basis of how patients were initiated on ezetimibe, and what happened after ezetimibe was added.

Eligibility to treatment with ezetimibe monotherapy requires a patient to meet the criteria set out in the General Statement on Lipid Lowering Drugs[9] as well as being contraindicated or intolerant to statins. Patients treated with ezetimibe monotherapy are assumed to have contraindications or documented

[9] http://www.pbs.gov.au/info/healthpro/explanatory-notes/gs-lipid-lowering-drugs

intolerance. This is reasonable, given that the fundamental role of statin therapies as first line agents is recognised and accepted universally by clinicians.

For patients to qualify for PBS reimbursement of ezetimibe as add-on treatment, they must first meet the definition of inadequate control with a statin. That is, lipid levels in excess of a particular threshold (described in the General Statement for Lipid Lowering Drugs) after at least three months of treatment at a maximum tolerated dose of a statin. It is assumed that all patients would exceed the relevant qualifying cholesterol threshold before accessing ezetimibe because otherwise they would be defined as controlled and not need further lipid lowering.

A 10% PBS concessional patient dataset (2010 to 2015) from Model Solutions was used to classify ezetimibe patients who fulfil their first ever EZETROL® script and/or their first ever ezetimibe FDC / co-pack script into the discrete categories (Error! Reference source not found.). The cohort covers concessional patients only, as most statin prices are now below the current general co-payment level of $38.30/script.

Table 7: EZETROL® and ezetimibe FDC / co-pack patient initiations and movements (2010-15)

Group	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Total**
	No previous statin use	Titrated up from lower statin dose	<3 historical statin Rx of same dose	<3 recent statin Rx of same dose	Met PBS criteria then up-titrated	3+ historical statin Rx of same dose	Meets PBS criteria	
VYTORIN®	413	177	93	146	471	712	3,411	5,423
ATOZET®	28	54	15	33	35	98	813	1,076
ROSUZET®	9	13	3	10	8	42	308	393
EZE mono							4,165	4,165
EZE + statin	45		6	152		387	3,161	3,751
Total	495	244	117	341	514	1,239	11,858	14,808
% of total	**3.3%**	**1.6%**	**0.8%**	**2.3%**	**3.5%**	**8.4%**	**80.1%**	**100.0%**
						88.5%		

Source: 10% PBS concessional patient dataset (2010 to 2015) from Model Solutions
Notes: Patients were classified as meeting the PBS criteria if they had received 3 scripts of a statin in the previous 12 months (Group 7). If the patient had received 3 scripts, but not all in the previous 12 months then they were classified in Group 6. This also represents use consistent with the PBS criteria, and probably represents less frequently managed patients and/or poorly persistent or compliant patients.
Abbreviations: EZE + statin = EZETROL® + statin; EZE mono = EZETROL® monotherapy

The analysis concludes that in 9 of 10 patients, PBS eligibility criteria for ezetimibe were adhered to.

Transitions in the remaining patients are somewhat inconclusive, as they could be an artefact of the limitations of the data / analyses, or may be the result of treatment changes based on the physicians' assessment of patient needs and clinical judgment. For example:

- Some concessional patient script records could be incomplete - this is because most statin scripts for general patients are under the PBS general co-payment level and some concessional patients could have been recent general patients

- There may be patients (such as recently arrived migrants or those who paid for statins via private script) who have been exposed to statins outside the PBS system for whom we have no record

- Subsequent up-titration of a statin (Group 2) could represent a circumstance where ezetimibe is added after patient has reached the maximally tolerated statin dose; the patient might still be uncontrolled and clinician might choose to re-challenge the patient with a higher statin dose

TOR 2: CLINICAL GUIDELINES

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

Approach: identify and review recent clinical guidelines for treatment of hypercholesterolaemia; review and compare these to the PBS restrictions presented and the utilization of ezetimibe.

Results: Australian guidelines published by NVDPA, NHF and RACGP were identified. In addition a recent guideline published by the American College of Cardiology was included in the review since it focussed on the use of non-statin therapies and was published after release of IMPROVE-IT results.

Management of cholesterol levels (e.g. targets for patients at high risk) is largely consistent with the general criteria for lipid lowering therapies. In regards to treatment of patients, the guidelines showed consistency with respect to the clinical placement of non-statin lipid lowering therapies such as ezetimibe – its use was restricted to circumstances where statins are contraindicated or not tolerated (monotherapy treatment), or where patients are not at target following use of maximally tolerated doses of a statin. The clinical placement of ezetimibe recommended in clinical guidelines is therefore consistent with the eligibility criteria for use of ezetimibe on the PBS.

The analyses of the longitudinal data presented in the submission in relation to TOR 1 conclude that the PBS eligibility criteria for ezetimibe are being adhered to.

Lastly, the guidelines confirm that in circumstances where:

- statins are not tolerated or are contraindicated, the therapy most likely to be used (aside from ezetimibe) is cholestyramine, making it the main comparator for ezetimibe monotherapy
- patients are not at target despite maximally tolerated doses of a statin, most patients would not be treated, making placebo the appropriate comparator for ezetimibe add-on therapy

Conclusions: use of ezetimibe is consistent with its PBS eligibility criteria, and the latter are in line with best practice clinical guidelines for the treatment of hypercholesterolaemia. Moreover, this review confirms that the main comparators accepted by the PBAC in past submissions (cholestyramine for ezetimibe monotherapy and placebo for ezetimibe add-on to a statin) are unchanged.

TOR 3: CLINICAL DATA AND COST EFFECTIVENESS

Purpose of TOR 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.

Approach: The clinical guidelines and PBS history confirmed that the evaluation required 2 distinct analyses relative to two different comparators – ezetimibe monotherapy compared to cholestyramine, and ezetimibe with statin compared to placebo. Two literature searches were conducted, and relevant clinical studies analysed and results compared.

Results: Systematic review of the literature confirms that long term patient relevant outcomes are only available for combination therapy, when ezetimibe is added to statin therapy. For monotherapy treatment, the approach taken was to review available evidence for surrogate measures, to assess whether conclusions made in the past need to be revised.

Combination with a statin: The IMPROVE-IT study was the only trial that fulfilled the search criteria and formed the basis for the submission. On the basis of this evidence ezetimibe added to statin therapy provided superior risk reduction for the primary and secondary endpoints.

The IMPROVE-IT population represented only a sub-population of the wider PBS population. It was therefore necessary to extrapolate the CV event reductions from the study to the wider population using the CTT meta-analysis of all major statin studies. The clinical benefit of ezetimibe when added to a stain provides a further 24% LDL-C reduction which is consistent with other eze/statin combination trials. This allows the modelling of the effect of ezetimibe on LDL-C linkage to CV outcomes via the CTT meta-analysis.

The PBAC previously accepted economic model (2003, 2006) was calibrated with the results of the IMPROVE-IT trial. The model accurately predicts CHD outcomes and therefore can be considered to be generalizable to a broader population.

The updated economic evaluation presented resulted in an incremental cost effectiveness of $[redacted] per life year gained. Thus ezetimibe remains a cost effective option as an add-on treatment.

Monotherapy treatment: In patients who are intolerant or who have contra-indications to statins there are no clinical outcomes data available. PBAC have previously recommended the use of ezetimibe in this patient group based on an indirect comparison to cholestyramine. The literature search was updated – no new clinical evidence was identified for cholestyramine; however 13 new ezetimibe trails were identified. The result was highly consistent with that in the original submission and therefore if follows that the therapeutic relativity should remain unchanged, that is ezetimibe 10mg = cholestyramine 17.2g daily.

An updated cost-minimisation analysis was presented that takes into account the 29% increase in the cost of the comparator. On the basis of this, the cost-minimisation analysis presented supported an increase in the price of ezetimibe monotherapy to $[redacted] / pack (AEMP).

The original price of ezetimibe was determined on the basis of a weighted price between the 2 patient populations (mono and add-on). Based on this updated analysis and a re-weighting to reflect current utilisation of mono vs add-on, the price for ezetimibe should be $[redacted].

Conclusions: recent trials (IMPROVE-IT) provide further supportive evidence that ezetimibe represents a cost effective therapy for patients. This review confirms that the ezetimibe has maintained its cost-effectiveness at a similar value to 2003 and 2006 as add-on therapy. The review also supports a higher price for ezetimibe as monotherapy.

MSD would reaffirm that the current price for ezetimibe be maintained at $[redacted]/ pack (AEMP). This should provide confidence to the PBAC that the use of ezetimibe continues to be cost effective.

Analysis of clinical evidence

The clinical evaluation for the review is presented in 2 populations:

1. As add-on treatment to statin
2. As monotherapy in patients intolerant or contraindicated to statin treatment.

Previously the PBAC recommendations have been based on the surrogate endpoint of LDL lowering. In the absence of patient relevant clinical outcomes lipid lowering has been an accepted measure of efficacy in the determination of cost effectiveness.

1. Add-on: The key clinical evidence is provided by the landmark IMPROVE-IT study. IMPROVE-IT was a large, multicenter, long-term study designed to assess the CV outcomes benefit of further LDL-C lowering through the addition of the cholesterol absorption inhibitor ezetimibe, to statin treatment in subjects at high risk for recurrent CV events.

IMPROVE IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) was a multicenter, double-blind, randomised study to establish the clinical benefit and safety of vytorin (ezetimibe/simvastatin tablet) vs simvastatin monotherapy in high-risk subjects presenting with acute coronary syndrome (ACS).

- **Main comparative effectiveness results of clinical evaluation**

When added to statin therapy, ezetimibe resulted in incremental lowering of LDL cholesterol levels (0.4mmol/L) and resulted in improved cardiovascular outcomes. Ezetimibe in combination with simvastatin produced a 6.4% reduction (HR 0.936; 95% CI 0.89-0.99; p=0.016) in the primary end point: composite of CV death, nonfatal MI unstable angina requiring hospitalisation coronary revascularisation or nonfatal stroke vs simvastatin.

Table 8: Effect of EZE/Simva versus Simva on Primary endpoint: IMPROVE-IT

n/N		Hazard Ratio (95% CI)	p-Value
EZE/Simva	**Simva**		
2572/9067 (32.7%)	2742/9077 (34.7%)	0.936 (0.89-0.99)	0.0016
Percentages are 7-year Kaplan–Meier estimates. Major coronary events included MI, hospitalization for unstable angina, and coronary revascularization 30 or more days after randomisation			

Data source: Cannon 2015 Table 2 pg 2393

Results for the secondary endpoints are included in the Table 9 below ..

Table 9: Effect of EZE/Simva versus Simva on Secondary endpoints: IMPROVE-IT

n/N		Hazard Ratio (95% CI)	p-Value
EZE/Simva (n=9067)	**Simva (n=9077)**		
• Death from any cause, major coronary event, or nonfatal stroke			
3089 (38.7%)	3246 (40.3%)	0.95 (0.90-1.0)	0.03
• Death from coronary heart disease, nonfatal MI, urgent coronary revascularization ≥30 days			
1322 (17.5)	1448 (18.9)	0.91 (0.85–0.98)	0.02
• Death from cardiovascular causes, nonfatal MI, hospitalization for unstable angina, all revascularization ≥30 days, nonfatal stroke			
2716 (34.5)	2869 (36.2)	0.95 (0.90–1.0)	0.04
Percentages are 7-year Kaplan–Meier estimates. Major coronary events included MI, hospitalization for unstable angina, and coronary revascularization 30 or more days after randomisation			

Data source: Cannon 2015 Table 2 pg 2393

- **Main comparative safety results of clinical evaluation**

In general, there were no meaningful differences in clinical adverse events between treatment groups. No significant between-group differences were seen in the percentage of patients who had elevations in alanine aminotransferase levels that exceeded three times the upper limit of the normal range or in the rates of gallbladder-related adverse events, cholecystectomy, muscle-related adverse events, or new, relapsing, or worsening cancer. Discontinuation of study medication owing to an adverse event occurred in 10.1% of the patients in the simvastatin-monotherapy group and in 10.6% of those in the simvastatin–ezetimibe group.

The addition of ezetimibe to statin therapy provided no meaningful increases in any specific adverse events.

- **Main comparative lipid measurements of clinical evaluation**

At the time of hospitalisation for the index event, the mean LDL cholesterol level was 93.8 mg per decilitre (2.4 mmol per litre) in each group. Among patients who had blood samples obtained at 1 year, the mean LDL cholesterol level was 69.9 mg per decilitre (1.8 mmol per litre) in the simvastatin-monotherapy group and 53.2 mg per decilitre (1.4 mmol per litre) in the simvastatin–ezetimibe group ($P<0.001$).

The relationship between LDL-C reduction and outcomes treatment benefit was assessed through analysis of observed reductions in CV events per 1.0 mmol/L reduction in LDL-C. This assessment facilitates comparison with observations from the 2010 Cholesterol Treatment Trialist meta-analysis (of 26 randomized statin trials with ~170,000 participants) where lowering LDL-C (assessed at 1 year in each trial) by 1 mmol/L (38.67 mg/dL) with statin therapy reduced the incidence of major vascular events by 22%.

The CTT-MVE endpoint was significantly reduced by ezetimibe/simvastatin/ezetimibe by 7.2% compared with simvastatin (HR 0.928, 0.879 – 0.980). The HR for clinical benefit per mmol of LDL-C reduction with ezetimibe in IMPROVE IT was 0.798 (95% CI 0.677 - 0.940), as compared with 0.78 observed with statins in the 2010 CTT meta-analysis.

2. Monotherapy: The basis for the PBAC recommendation was an indirect comparison of ezetimibe monotherapy to cholestyramine monotherapy using placebo as the common comparator. In the updated literature search no new patient relevant outcome studies were retrieved. On this basis the LDL reduction comparison as an acceptable surrogate endpoint (as recommended in 2003) was updated. The meta-analysis was used to re-establish the equi-effective daily doses.

The percent change from baseline in LDL-c from the original submission was -19.2% (95% CI -20.5, -17.9). The analysis was based on 2 large randomised controlled trials with a total of 1719 patients. The meta-analysis presented in the NICE submission, which included results from an additional 13 trials with 4058 participants, demonstrated a small improvement in LDL-c lowering capacity compared with the 2003 analysis (-20.4%, 95% CI -21.6, -19.3). As no new evidence was identified, the effect of cholestyramine treatment on LDL-c lowering remains unchanged from the original 2003 PBAC submission, i.e. -20.5% (-21.3, -19.6).

While the result from the updated meta-analysis is numerically better than the result from the original submission the significant overlap in the 95% CI across the two estimates suggests the difference is unlikely to be statistically different.

Thirteen new ezetimibe trials were identified and included in the meta-analysis. The result of which was highly consistent with the original analysis, and while numerically better it is unlikely to represent a statistically significant improvement. Therefore, taking a conservative approach, the estimate of effect provided in the original PBAC submission remains the best available evidence.

Given there is no basis for changing the conclusions regarding the comparative benefit of ezetimibe relative to cholestyramine, it follows that the therapeutic relativity should remain unchanged, that is Ezetrol 10 mg daily = cholestyramine 17.2 g daily.

Therapeutic conclusions and types of economic evaluation presented

On the basis of the evidence from the 2 analyses:

- Ezetimibe in combination with simvastatin is superior in terms of efficacy in reducing CV events versus simvastatin.

- Ezetimibe in combination with simvastatin is similar in terms of safety and tolerability versus simvastatin.

  the most appropriate form of economic evaluation in this patient population is a cost effectiveness analysis

- Ezetimibe as monotherapy produces LDL lowering non-inferior to cholestyramine as determined by indirect analysis

- Ezetimibe as monotherapy appears to be superior in terms of safety and tolerability versus cholestyramine but is not quantifiable

  The most appropriate form of economic evaluation in this patient population is a cost minimisation analysis

Reviewing the cost effectiveness of ezetimibe

The translation issues identified and assessed in Section C relate directly to the terms of reference of this review with respect to the pivotal clinical study reporting on long term patient relevant outcomes, IMPROVE-IT, and the implications of this study on the cost-effectiveness of ezetimibe.

The cost-effectiveness of ezetimibe has, to date, been based on the translation of improvements in lipid profiles to patient relevant outcomes. Specifically, this has involved the "(transformation of) TC:HDL ratios to CHD events, deaths due to CVD and mortality and estimates LYG and QALY." (March 2009 PSD). The economic model used to assess the cost-effectiveness of ezetimibe has remained largely unchanged throughout various submissions to the PBAC which have examined the cost-effectiveness of ezetimibe in a series of different patient population with varying baseline characteristics.

To this end, data from the IMPROVE IT trial offers the opportunity to test the validity of the economic modelling which has supported the PBS listing of ezetimibe since 2003. That is, should the economic model accurately predict 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.

This is important because, the population in the IMPROVE IT trial is not representative of the patient population who use ezetimibe on the PBS. Most notably the IMPROVE IT trial did not include a threshold minimum lipid level and nor did it require patients to be first treated with statins.

Pre-modelling studies to generate variables for incorporation into a modelled economic evaluation

Section C presents two main pre-modelling studies. Firstly, Section C.1 undertakes a calibration of the model to the IMPROVE-IT trial. This calibration determines the extent to which the model deviates from the results of IMPROVE-IT for a given set of model inputs (that is, the patient characteristics and lipid efficacy observed in the trial). This pre-modelling study shows that the model slightly underestimates the incidence of CHD events compared to the rates observed in the IMPROVE-IT trial. Importantly, the differences in lipid profiles between treatment groups in the model did accurately predict differences in the incidence of events. Therefore the economic model reflects accurately the incremental cost-effectiveness of ezetimibe.

Secondly, Section C.2 examines the applicability of the patient population and circumstances of use of ezetimibe in the IMPROVE-IT trial to determine the appropriate patient population and treatment efficacy with which to assess the cost-effectiveness of ezetimibe on the PBS. The IMPROVE-IT population is different to the PBS population in terms of both patient characteristics and circumstances of use.

Economic evaluation for main indication – cost-effectiveness analysis

Table 10 summarises the evolution of the economic model and consequent PBAC decision making with respect to ezetimibe since it was first recommended in late 2003.

In 2003, ezetimibe was accepted for listing in patients with CHD and/or diabetes at a dispensed price of $74.02 and an incremental cost per life year gained of $23,996.

In 2005 and 2006, this listing was extended to include patients with CVD, PVD, heterozygous familial hypercholesterolaemia, hypertension and/or a family history of CHD. The incremental cost per life year gained in these populations ranged from $27,000 to $42,000 per life year gained. These populations are at lower overall risk of CHD events than the original CHD/diabetes population and the slightly higher incremental cost-effectiveness ratios reflect this. The price of ezetimibe did not change over these submissions. Therefore, this cost-effectiveness review is essentially reviewing the conditions and cost-effectiveness of the 2003 and 2006 submissions.

Table 10: Ezetimibe PBAC submission history

Model feature	Dec 2003 model	Nov 2005 model	Nov 2006 model	Current
Patient population	CHD and/or diabetes (with TC >4 after maximum tolerated statin treatment)	Addition of patients with CVD, PVD, HeFH (with TC >4 after maximum tolerated statin treatment)	Addition of patients with hypertension, family history of CHD (with TC >4 after maximum tolerated statin treatment)	As per the November 2006 population and circumstances of use
Population data included in the economic model	SCOPE	SCOPE	SCOPE	BEACH SAND
Comparison	EZE + Statin vs Statin	EZE + Statin vs Statin	EZE + Statin vs Statin	EZE + Statin vs Statin
% change in TC-HDL	-19.18% vs -3.27%[1]	-19.18% vs -3.27%[1]	-19.54% vs -2.55%[5]	-19.54% vs -2.55%[5]
Ezetimibe price (ex-man; add-on component)	[redacted]			
Incremental cost per life year gained ratios	CHD: $21,417[3] Diabetes: $23,803[3] All: $23,996[2]	CVD: $27,208[3] PVD: $23,803[3] HeFH: $42,307[3]	Family history: $37,100[3] Hypertension: $31,646[3]	All patients: $24,256 (see **Error! Reference source not found.** to follow)

[1] P02173/P02246 Ezetimibe Add-On Study (see December 2003 PBAC submission
[2]EZETROL draft minutes DEC 2003
[3]EZETROL_VYTORIN_ESC ADV_PART A
[4]PBS website: http://www.pbs.gov.au/medicine/item/8757X
[5] Based on a meta-analysis of six trials where ezetimibe was compared with placebo as add-on therapy to a statin. See ezetimibe November 2006 public summary document.

It therefore follows that ezetimibe remains as cost-effective as it was when it was first listed.

Cost per patient per year (chronic therapy)

The cost per patient per year is presented in Table D.4-2.1 of Section D.4 of the main submission. The costs per patient per year for the treatments in the economic evaluations are:

- EZE/SIMVA: $832.57 ($2.28 per day, $68.43 per PBS item)

- SIMVA: $164.37 ($0.45 per day, $13.51 per PBS item)

Adding ezetimibe to statin is associated with a better lipid profile compared a statin alone. This translates into fewer CHD events and lower costs associated with these events. The economic evaluation includes the hospital costs of these events. The unit cost per CHD event applied in the economic evaluation and a summary of the costs calculated in the base case of the economic evaluation are presented in Table 11.

Table 12 below shows that the incremental cost of ezetimibe was partially offset by savings in the cost of CHD events.

Table 11: Unit costs of CHD events applied in the economic evaluation (Cross reference to main submission: Table D.4.3-1)

Event	Cost per event
CHD death	$5,851
Non-fatal MI	$32,484
Other non-fatal CHD events	$27,167

Table 12: Lifetime costs estimated in the economic evaluation by treatment group and resource item (Cross reference to main submission: Table D.5.2-1)

Cost parameter	EZE	SIM	Difference
Ezetimibe costs	$7,603	$0-	$7,603
Statin costs	$1,501	$1,453	$48
CHD event costs	$4,112	$4,667	-$555
Total	$13,216	$6,120	$7,097

Net present value of the overall incremental effectiveness in the base case of the economic evaluation

The expected number of CHD events and the proportion of patients experiencing a CHD fatality in each treatment arm is presented in . The improved TC:HDL associated with adding ezetimibe to a statin translates to fewer fatal and non-fatal CHD events, which in turn translate to more life years and quality adjusted life years relative to treating with a statin alone.

Table 13: Life years and quality adjusted life years estimated in the economic model for each treatment group (Cross reference to main submission: Table D.5.3-1)

Parameter	EZE	SIM	Difference
All-cause mortality	1.0000	1.0000	0.0000
Fatal CHD events	0.3540	0.4008	-0.0468
Non–fatal CHD events	0.1253	0.1392	-0.0139
CHD events	0.4793	0.5400	-0.0607
Life years (undiscounted)	13.1416	12.5902	0.5514
Life years (discounted)	9.1324	8.8398	0.2926
QALYs (discounted)	8.8037	8.5199	0.2838

Base case results of the economic evaluation

The incremental cost per LYG for the base-case analysis is $24,256. This result suggests using ezetimibe as an add-on treatment for patients treated with statin remains a cost-effective second line option for the treatment of hypercholesterolaemia.

Table 14: Incremental cost-effectiveness of EZE/Simva compared to SIMVA (Cross reference to main submission: Table D.5.1-1)

Item	EZE	SIM	Difference
Cost	$13,216	$6,120	$7,097
Life years	9.1324	8.8398	0.2926
QALYs	8.8037	8.5199	0.2838
IC/LYG			$24,256
IC/QALY			$25,010

Stepped economic evaluation

A trial based economic evaluation of the IMPROVE-IT trial can be approximated using the economic model itself with the following assumptions:

- baseline IMPROVE IT population patient characteristics
- apply the change in TC:HDL observed in IMPROVE IT of –22.5% vs –12.4% in the ezetimibe and placebo arms respectively
- apply the CHD event calibration factor of 1.11
- model duration of 6 years (that is, disregarding the first year of IMPROVE IT)

A stepped economic evaluation can then be presented by relaxing these assumptions at each step. The stepped economic evaluation in Table 15 moves from this trial based analysis to the base case results of the economic model. The incremental cost effectiveness is expressed as the incremental cost per life year gained (LYG) for this analysis for ease of comparison with ICERs of previous submissions.

Table 15: Results of the stepped economic evaluation (Cross reference to main submission: Table D.5.4-1)

Step	Incremental cost per LYG
Trial based (IMPROVE-IT)	$107,403
Use BEACH SAND population	$115,236
Use add-on efficacy values (-19.5% v 2.6%)	$66,804
Remove the calibration factor	$72,297
Extrapolate from 6 years to lifetime model	$24,256