PUBLIC SUMMARY DOCUMENT
Product: Ezetimibe, tablet, 10 mg, Ezetrol®
Sponsor: Merck Sharp and Dohme (Australia) Pty Ltd
Date of PBAC Consideration: November 2010

1. Purpose of Application

The submission requested that the definition of 'inadequate control with a statin' in the current restriction be extended to allow patients to add ezetimibe to lower doses of rosuvastatin or atorvastatin.

2. Background

At the June 2003 meeting, the PBAC recommended an Authority required listing for ezetimibe for: (1) patients eligible to receive lipid lowering medication when statins were unsuitable or contraindicated; (2) homozygous sitosterolemia; and
(3) patients with homozygous familial hypercholesterolemia in combination with a statin.

At its December 2003 meeting, the PBAC recommended listing ezetimibe, co-administered with a statin, in patients eligible for subsidised lipid lowering medication, with coronary heart disease and/or diabetes mellitus, when the patient is above National Hearth Foundation target lipid levels in this patient group, despite at least 3 months treatment at a dose of 40 mg daily or greater of a statin, on the basis of acceptable cost-effectiveness. At this meeting, listing for heterozygous familial hypercholesterolemia was rejected. Ezetimibe was first PBS listed on 1 August 2004.

At the November 2005 meeting, the PBAC recommended the addition of two indications to the listing for ezetimibe, namely, peripheral vascular disease and heterozygous familial hypercholesterolemia, on the basis of acceptable cost-effectiveness in these patient groups. These changes were effective 1 April 2006.

At the November 2006 meeting, the PBAC recommended extending the Authority required listing for ezetimibe to include the treatment of patients with hypertension or a family history of coronary heart disease in patients whose cholesterol levels are inadequately controlled with a statin according to the current ezetimibe PBS restriction definitions of inadequate control. The change was effective 1 August 2007.

At its November 2009 the PBAC rejected an application to change the current 'Authority Required (Streamlined)' listing for ezetimibe to a 'Restricted Benefit' listing on the grounds that the more restrictive classification remained appropriate.

3. Registration Status

Ezetimibe is TGA registered for:

- Primary hypercholesterolaemia: administered alone, or with an HMG-CoA reductase inhibitor (statin), as adjunctive therapy to diet.
- Homozygous Familial Hypercholesterolaemia: administered with a statin
- Homozygous Sitosterolaemia (Phytosterolaemia)

4. Listing Requested and PBAC's View

The change requested was an amendment to the definition of 'inadequate control with a statin' in the restriction wording. The proposed amendments are highlighted below in bold.

Authority required (STREAMLINED)
Treatment, in conjunction with dietary therapy and exercise, for co-administration with an HMG CoA reductase inhibitor (statin) in patients whose cholesterol levels are inadequately controlled with a statin and who have:
(a) coronary heart disease; or
(b) diabetes mellitus; or
(c) peripheral vascular disease; or
(d) heterozygous familial hypercholesterolaemia; or
(e) symptomatic cerebrovascular disease; or
(f) family history of coronary heart disease; or
(g) hypertension.

Inadequate control with a statin is defined as follows:
(1) where the patient falls into a category for which the General Statement for Lipid-Lowering Drugs includes an initial cholesterol threshold for PBS-subsidy, a cholesterol level in excess of that threshold after at least 3 months of treatment at a daily dose of **20 mg or greater of rosuvastatin or atorvastatin or 40 mg or greater of any other statin**, in conjunction with dietary therapy and exercise. The dose and duration of statin treatment and the cholesterol level which shows inadequate control must be documented in the patient's medical records when ezetimibe is initiated. The cholesterol level which shows inadequate control must be no more than 2 months old when ezetimibe is initiated; or
(2) where the patient falls into a category for which the General Statement for Lipid-Lowering Drugs allows PBS-subsidised treatment with a statin at any cholesterol level, a cholesterol level in excess of 4 mmol per L after at least 3 months of treatment at a daily dose of **20 mg or greater of rosuvastatin or atorvastatin, or 40 mg or greater of any other statin**, in conjunction with dietary therapy and exercise. The dose and duration of statin treatment and the cholesterol level which shows inadequate control must be documented in the patient's medical records when ezetimibe is initiated. The cholesterol level which shows inadequate control must be no more than 2 months old when ezetimibe is initiated.

Authority required (STREAMLINED)
Patients eligible for PBS-subsidised lipid-lowering medication (according to the criteria set out in the General Statement for Lipid-Lowering Drugs) where treatment with an HMG CoA reductase inhibitor (statin) is contraindicated;

Patients eligible for PBS-subsidised lipid-lowering medication (according to the criteria set out in the General Statement for Lipid-Lowering Drugs) where treatment with an HMG CoA reductase inhibitor (statin) must be discontinued or reduced to a dose of 20 mg or less per day, because the patient developed a clinically important product-related adverse event during treatment with a statin.
A clinically important product-related adverse event is defined as follows:
(i) Severe myalgia (muscle symptoms without CK elevation) which is proven to be temporally associated with statin treatment; or

(ii) Myositis (clinically important CK 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.

Authority required (STREAMLINED)
Homozygous sitosterolaemia;
Patients with homozygous familial hypercholesterolaemia who are eligible for PBS-subsidised lipid-lowering medication (according to the criteria set out in the General Statement for Lipid-Lowering Drugs), in combination with an HMG CoA reductase inhibitor (statin).

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

The submission claimed that the requested restriction wording change was to acknowledge that rosuvastatin and atorvastatin are more potent than the other PBS subsidised statins as evidenced by the establishment of two separate therapeutic groups and the submission also claimed that better LDL-C reductions are observed when adding ezetimibe compared with up-titrating the statin dose.

6. Comparator

The submission nominated placebo as the main comparator as it claimed that patients inadequately controlled on either atorvastatin 20 mg or rosuvastatin 20 mg in most instances have no change in therapy; up-titration to the 40 mg dose was used as a secondary comparator. The PBAC considered that the secondary comparison was the more relevant. *See Recommendation and Reasons.*

7. Clinical Trials

The basis of the submission was:

- One direct randomised trial comparing up titration to atorvastatin 40 mg (A40) versus addition of ezetimibe 10 mg in patients with uncontrolled cholesterol despite receiving treatment with atorvastatin 20 mg (A20) (Trial 079), patients who were not taking A20 at enrolment were all treated with A20 for at least 5 weeks, those with elevated LDL-C at the end of run-in phase were randomised.
- One direct randomised trial comparing efficacy of A40 versus A20 plus ezetimibe 10 mg in patients with elevated LDL-C and triglycerides despite strict diet control (Trial 0692) (patients' prior lipid lowering agents were washed out during the screening phase, a strict diet was also initiated in all patients followed by a single blinded placebo run in phase).
- One direct randomised open label trial of rosuvastatin 40 mg (R40) versus R40 plus ezetimibe 10 mg (EXPLORER). Patients were required to discontinue lipid-lowering therapy before entering a 6-week dietary lead-in period. At the end of the run-in phase, eligible patients were then randomised.

Details of the published trials presented in the submission are shown in the table below.

Trial ID/First author	Protocol title/ Publication title	Publication citation
Trial 079 Conard S, et al.	Efficacy and safety or ezetimibe added to atorvastatin (20 mg) versus up-titration of atorvastatin (to 40 mg) in hypercholesterolaemic patients at moderately high risk for coronary heart disease.	*Am J Cardiol* 2008; 102: 1489-1494.
Trial 0692 Ballantyne C, et al.	Effect of ezetimibe co administered with atorvastatin in 628 patients with primary hypercholesterolemia. A prospective, randomised, double-blind trial.	*Circulation* 2003; 107: 2409-2415.
EXPLORER Ballantyne C, et al.	Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study).	*Am J Cardiol* 2007; 99: 673-680.

For PBAC's views on these trials, see Recommendation and Reasons.

8. Results of Trials

The efficacy of the treatment groups in the economic analysis was measured by the percentage change in LDL-C and HDL-C. Results from Trial 0692 were supportive only and were not used in the modelled economic evaluation.

The results of percentage reduction in LDL-C from baseline to 6 and 12 weeks is summarised in the table below. Percentage change in LDL-C was the primary endpoint in Trials 079 and 0692 but was only a secondary outcome in the EXPLORER trial.

Results of percent LDL-C reduction from baseline to either 6 or 12 weeks from the direct randomised trials

Trial	Treatment mean % change	Comparator mean % change	Weighted mean difference (95% CI)
A20 + EZE versus A40 at 6 weeks			
Trial 079 [a]	-31 (-35, -27[d]) N=92	-11 (-15, -7 [d]) N=92	**-20 (-26, -14)**
A20 + EZE versus A40 at 12 weeks			
Trial 0692 [a c]	-53.7 (1.9[e]) N=62	-43.1 (1.9 [e]) N=66	**-10.6 (-15.8, -5.4)**
R40 + EZE versus R40 (aka placebo) at 6 weeks			
EXPLORER [b]	-69.8 (NR) N=235	-57.1 (NR) N=230	**-12.7 (NR)** **P<0.0001**

Abbreviations: A20 = atorvastatin 20 mg, EZE = ezetimibe 10 mg, A40 = atorvastatin 40 mg; R40 = rosuvastatin 40 mg. Bold typography indicates statistically significant differences

[a] primary outcome in the trial
[b] secondary outcome in the trial
[c] use direct LDL-C results
[d] 95% CI
[e] standard error mean (SEM)

At 6 weeks, there was a statistically significant difference in percentage reduction in LDL-C from baseline between A20 plus ezetimibe and R40 plus ezetimibe compared with A40 or R40 (i.e. placebo) respectively. At 12 weeks (Trial 0692), there was a

statistically significant difference in percentage reduction in LDL-C for patients treated with A20 plus ezetimibe compared with A40.

The results of percent increase in HDL-C from baseline to 6 or 12 weeks from the direct randomised trials showed that at 6 weeks, there was no statistically significant difference in percentage increase in HDL-C from baseline between A20 plus ezetimibe and R40 plus ezetimibe compared with A40 or R40 (i.e. placebo) respectively, weighted mean difference (95 % CI): 2 (-2, 6) and 2 (NR) p value = 0.151 respectively. At 12 weeks (Trial 0692) however there was a statistically significant greater increase in HDL-C for patients treated with A20 plus ezetimibe compared with A40, WMD (95 % CI): 5.5 (1.4, 9.5).

The PBAC noted that no significant toxicity signals had emerged with use of ezetimibe.

There were no statistically significant different adverse events between any of the treatment and comparator arms from the randomised trials. It was noted that in the EXPLORER trial, there was one death reported in the combination therapy arm of ezetimibe plus rosuvastatin 40 mg (acute myocardial infarction) but this was not considered to be treatment related.

The submission provided additional data on potential safety concerns beyond those identified in the clinical trials. The submission concluded from the Ezetimibe Periodic Safety Update Report (PSUR) that overall no new safety issues associated with long term use were identified during this reporting period. The submission also discussed the results of the U.S Food and Drug Administration (FDA) conducted review (December 2009) investigating the findings from the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial, which showed that more subjects treated with ezetimibe and simvastatin combination developed and died from all types of cancer when compared with those taking placebo during the five-year study. The completed FDA review included an interim analysis (Peto et al. 2008) of two ongoing studies with ezetimibe: the Study of Heart and Renal Protection (SHARP) and the Improved Reduction in High-Risk Subjects Presenting with Acute Coronary Syndrome (IMPROVE-IT) trial. This analysis found that in the SEAS trial new onset of cancer was higher in the ezetimibe plus simvastatin arm compared with the control group (101 versus 65; uncorrected p value = 0.006) from several cancer sites. However, when the SHARP and IMPROVE-IT studies were combined there was no overall excess of cancer (313 active-treatment group versus 326 control; risk ratio 0.96; 95 % CI 0.82 to 1.12; p = 0.61). The SHARP trial is expected to be completed in 2010 and IMPROVE-IT in 2013.

9. Clinical Claim

The submission claimed the addition of ezetimibe to 20 mg of rosuvastatin or atorvastatin as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over up titration of the statin or not changing the treatment (i.e. placebo comparison).

The PBAC considered that the requested change was consistent with clinical practice and the quality use of medicines.

10. Economic Analysis

A stepped economic evaluation was presented. The submission presented two economic evaluations: one for a population treated with atorvastatin 20 mg and one for a population treated with rosuvastatin 20 mg.

The economic evaluation was a cost-utility analysis.

The modelled economic evaluation was a lifetime model and patients were followed until death. At the same time, the model assumed that the benefits of treatment were maintained for the patient's lifetime. It was uncertain whether a time horizon of 70 years as the base case was reasonable, given the starting age of 71 years and health status of the population in the modelled evaluation.

For both the A20 and R20 populations, the results of the stepped economic evaluation calculated the incremental cost per extra quality adjusted life year (QALY) gained to be $15,000 - $45,000.

The results of the univariate sensitivity analyses indicated that the model was most sensitive to the model duration.

For PBAC's view on the economic analysis, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients per year to be in the range of 10,000 to 50,000 in Year 5 of listing. The financial cost per year to the PBS was estimated in the submission to be less than $10 million in Year 5. The submission's estimates were considered uncertain due to uncertain estimates for annual growth rates and the proportion of uncontrolled A20 patients assumed to remain uncontrolled due to prescriber's choosing to 'do nothing'.

12. Recommendation and Reasons

The PBAC recommended that the restriction for ezetimibe be amended to incorporate wording that did not specify a particular dose of a statin be prescribed to achieve an appropriate lowering of cholesterol, rather the wording should stipulate a three month trial with the maximum tolerated dose of a statin. This option allows ezetimibe to be added as clinically appropriate while continuing to promote up-titration of statins as the first line treatment of hypercholesterolaemia. Despite the considerable deficiencies in both clinical and economic data presented, the PBAC considered that such a change is also consistent with clinical practice and quality use of medicine and represented acceptable, if somewhat uncertain, cost effectiveness in this patient group with inadequate cholesterol control.

The PBAC noted that the submission nominated placebo as the main comparator as it claimed that patients inadequately controlled on either atorvastatin 20 mg or rosuvastatin 20 mg in most instances have no change in therapy; up-titration to the 40 mg dose is used as a secondary comparator. The PBAC considered that the secondary comparison was the more relevant. The PBAC agreed that for both R20 and A20, placebo is not the most likely treatment to be replaced by ezetimibe. Both Medicare data and the Cegedim Strategic Data survey data suggest that the majority of hyperlipidaemia patients who do not change therapy despite being uncontrolled on A20 or R20 are unlikely to alter their

therapy due to the listing of ezetimibe. The majority of the remaining patients are currently up-titrating to either a higher dose of rosuvastatin or atorvastatin.

None of the trials that formed the basis of the submission were fully representative of the requested restrictions. Trial 079, although closest to the requested listing (i.e. in a population of patients whose cholesterol is inadequately controlled on A20), is based on uncontrolled cholesterol levels after only 5 weeks of treatment with A20 in some patients. The PBS definition of uncontrolled cholesterol is after a minimum of 3 months of treatment for all patients. Trials 067 and EXPLORER, although comparing the relevant therapeutic agents, required patients to washout their prior lipid lowering agents and as a result patients were not taking lipid-lowering agents at randomisation. Therefore these trials examined the efficacy of first line treatments of hypercholesterolemia and differ to the very specific second line listing requested in this submission for patients whose cholesterol levels are inadequately controlled with A20 or R20. In addition, the dose of rosuvastatin used in the EXPLORER trial is greater than that for which listing was requested (R40 rather than R20).

The PBAC agreed that there was uncertainty about whether the results of the trials are representative of the true likely effect of ezetimibe 10 mg added to either A20 or R20 compared with up-titration in patients' whose cholesterol is inadequately controlled as defined by the requested restriction. For example, although the results of percentage reductions in LDL-C indicate superiority of ezetimibe over up-titrated statin, patients may not have received an adequate trial of A20 prior to randomisation. Furthermore, the percentage LDL-C reduction was measured after only 6 weeks of treatment in Trial 079 and EXPLORER, this is half the duration required by the requested listings to determine adequate response to lipid lowering therapy. The EXPLORER trial also compared addition of ezetimibe to placebo which as indicated above, is not an appropriate comparison.

In addition, at 6 weeks, there was no statistically significant difference in percentage increase in HDL-C from baseline between A20 plus ezetimibe and R40 plus ezetimibe compared with A40 or R40 (i.e. placebo) respectively, weighted mean difference (95 % CI): 2 (-2, 6) and 2 (NR) p value = 0.151 respectively. At 12 weeks (Trial 0692) however there was a statistically significant greater increase in HDL-C for patients treated with A20 plus ezetimibe compared with A40, WMD (95 % CI): 5.5 (1.4, 9.5).

The PBAC noted that no significant toxicity signals had emerged with use of ezetimibe.

The PBAC also noted a number of uncertainties in the economic evaluation and utilisation estimates. On balance the PBAC did not consider that changing the restriction would result in any additional net costs to the PBS.

Recommendation
EZETIMIBE, tablet, 10 mg

Amend the current restriction to read as follows:

Restriction: <u>Authority required (STREAMLINED)</u>
To be finalised

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor has no further comment.