**PUBLIC SUMMARY DOCUMENT**

**Product:** Ezetimibe and Atorvastatin, pack containing 30 tablets ezetimibe 10 mg, and 30 tablets atorvastatin 10 mg (as calcium), atorvastatin 20 mg (as calcium), atorvastatin 40 mg (as calcium) or atorvastatin 80 mg (as calcium), Atozet Composite Pack®
**Sponsor:** Merck Sharp and Dohme (Australia) Pty Ltd
**Date of PBAC Consideration:** July 2012

## 1. Purpose of Application

1) To request an Authority Required (STREAMLINED) listing for the treatment, in conjunction with dietary therapy and exercise, for co-administration of ezetimibe with an HMG CoA reductase inhibitor (statin) in patients whose cholesterol levels are inadequately controlled with a statin and who meet certain criteria or who have homozygous familial hypercholesterolaemia.

   *The request to list the fixed dose combination product was withdrawn by the sponsor.*

2) To Request PBAC advice of exempt item status under subsection 101(4AC) of section 84AH of the *National Health Act 1953.*

## 2. Background

The combination pack of ezetimibe with atorvastatin had not been considered previously by the PBAC. However the individual components are available on the Pharmaceutical Benefits Scheme (PBS).

## 3. Registration Status

Ezetimibe with atorvastatin was considered under the Therapeutic Goods Administration (TGA) and Pharmaceutical Benefits Advisory Committee (PBAC) parallel process. At the time of PBAC consideration, no TGA documentation was available.

## 4. Listing Requested and PBAC's View

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 the maximum tolerated dose of a 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 the maximum tolerated dose of a 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 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).

Prescribing by Medical Practitioners and Nurse Practitioners was requested.

*For PBAC's view, see Recommendation and Reasons.*

## 5. Clinical Place for the Proposed Therapy

The sponsor claimed that the combination of ezetimibe with atorvastatin will replace the individual components being used together for patients whose cholesterol is inadequately controlled with a statin or have homozygous familial hypercholesterolaemia.

## 6. Comparator

The submission nominated the corresponding doses of the components (ezetimibe and atorvastatin) given concomitantly as the main comparator. The submission also nominated ezetimibe with simvastatin as a secondary comparator. The PBAC considered both comparisons were relevant to a consideration of an ezetimibe with atorvastatin combination pack (co-pack).

## 7. Clinical Trials

The submission presented one randomised controlled trial (Protocol 0692) comparing the co-administration of ezetimibe and atorvastatin versus the therapies taken individually. The trial enrolled 373 patients with hypercholesterolaemia, however the included patients were not required to be uncontrolled on maximum tolerated doses of statins and patients with coronary heart disease, diabetes mellitus and peripheral vascular disease were excluded from the trial, in contrast to the requested restriction. The primary outcome of the trial was calculated LDL-C reduction (via the Friedewald calculation).

The submission also presented an indirect comparison of the co-administration of ezetimibe and atorvastatin versus the ezetimibe/simvastatin fixed dose combination (FDC), using placebo as the common reference. This comparison was conducted using data from Protocol 0692 (for the co-administration of ezetimibe and atorvastatin) and Protocol 038 (for the ezetimibe/simvastatin FDC). Protocol 038 enrolled 1,511 patients, however, only patients treated with placebo and the 10/20, 10/40 and 10/80mg ezetimibe/simvastatin FDC doses were considered by the submission (n=605). Like Protocol 0692, Protocol 038 did not

require patients to be uncontrolled on maximum tolerated doses of statins and patients with coronary heart disease, diabetes mellitus, peripheral vascular disease and cerebrovascular disease which have become symptomatic were excluded from the trial. Although the baseline characteristics were comparable between the trials, limited information was provided for Protocol 038 to allow for a proper assessment of the comparability of the populations and whether they were sufficiently comparable to inform a meaningful indirect comparison.

The table below details the published trials in the submission.

| Trial ID/Author | Protocol title/Publication Title | Publication Citation |
|---|---|---|
| **Comparison of co-administered ezetimibe and atorvastatin versus the therapies given individually** | | |
| Protocol 0692 (Ballantyne 2003) | Clinical Study Report: A Phase 3, Double-Blind Efficacy and Safety Study of Ezetimibe (SCH 58235) 10 mg in Addition to Atorvastatin Compared to Placebo in Subjects with Primary Hypercholesterolemia<br>Ballantyne CM, Houri J, Notarbartolo A, Melani L, Lipkia LJ, Suresh R, Sun S, LeBeaut AP, Sager PT, Veltri EP for the EZE Study Group. Effect of Ezetimibe Coadministered With Atorvastatin in 628 Patients With Primary Hypercholesterolemia. A Prospective, Randomized, Double-Blind Trial. | October 2001<br>*Circulation* 2003; 107:2409-2415 |
| Protocol 2154 (Ballantyne 2004) | Ballantyne CM, Blazing MA, King TR, Brady WE and Palmisano J. Efficacy and Safety of Ezetimibe Co-Administered With Simvastatin Compared With Atorvastatin in Adults With Hypercholesterolemia. | *American Journal of Cardiology* 2004;93:1487–1494 |
| Cruz Fernandez 2005 | Cruz-Fernandez JM, Bedarida GV, Adgey J, Allen C, Johnson-Levonas AO and Massaad R. Efficacy And Safety Of Ezetimibe Co-Administered With Ongoing Atorvastatin Therapy In Achieving Low-Density Lipoprotein Goal In Patients With Hypercholesterolemia And Coronary Heart Disease. | *International Journal of Clinical Practice*, June 2005, 59, 6, 619–627 |
| Blagden 2007 | Blagden MD and Chipperfield R. Efficacy and safety of ezetimibe co-administered with atorvastatin in untreated patients with primary hypercholesterolaemia and coronary heart disease. | *Current Medical Research and Opinion* Vol. 23, No. , 2007, 767–775 |
| **Indirect comparison of co-administered ezetimibe and atorvastatin versus the ezetimibe/simvastatin FDC (Vytorin®)** | | |
| Ezetimibe + atorvastatin trials | | |
| Protocol 0692 | See above | See above |
| Ezetimibe/simvastatin (Vytorin®) trial | | |
| Protocol 038 | Bayes HE, Ose L, Fraser N, Tribble D, Quinto K, Reyes R, Johnson-Levonas A, Sapre A, Donahue S, for the EZE Study Group. A Multicentre, Randomized, Double-Blind, Placebo-Controlled, Factorial Design Study to Evaluate the Lipid-Altering Efficacy and Safety Proifle of the Ezetimibe/Simvastatin Tablet Compared with Ezetimibe and Simvastatin Monotherapy in Patients with Primary Hypercholesterolemia. | *Clinical Therapeutics* 204, 26:1758-1773 |

Abbreviations: OL =Open Label, FMI = Final Market Image, FDC = Fixed Dose Combination, R = Randomised, A = Atorvastatin; EZE = Ezetimibe

## 8. Results of Trials

The results of the comparison of co-administered ezetimibe and atorvastatin versus the therapies taken individually are summarised in the table below (Direct LDL-C, total cholesterol and HDL-C reported in Protocol 0692 from baseline to 12 weeks).

| | E10 + A10 | E10 + A20 | E10 + A40 | E10 + A80 |
|---|---|---|---|---|
| **LDL-C (mmol/L)** | | | | |
| WMD (95% CI) from statin* | **-14.92 (-20.18, -9.66)** | **-13.93 (-19.23, -8.63)** | **-11.28 (-16.47, -6.09)** | **-8.34 (-13.60, -3.09)** |
| WMD (95% CI) from E10 | **-31.94 (-37.07, -26.81)** | **-35.27 (-40.45, -30.09)** | **-35.90 (-41.08, -30.73)** | **-41.27 (-46.45, -36.09)** |
| **Total cholesterol (mmol/L)** | | | | |
| WMD (95% CI) from statin* | **-12.19 (-16.43, -8.03)** | **-9.36 (-13.56, -5.16)** | **-9.20 (-13.31, -5.10)** | **-5.51 (-9.68, -1.35)** |
| WMD (95% CI) from E10 | **-24.45 (-28.61, -20.29)** | **-25.69 (-29.80, -21.58)** | **-28.16 (-32.25, -24.07)** | **-32.14 (-36.26, -28.02)** |
| **HDL-C (mmol/L)** | | | | |
| WMD (95% CI) from statin* | 2.55 (-1.52, 6.61) | **5.26 (1.14, 9.37)** | 0.82 (-3.19, 4.83) | 3.74 (-0.34, 7.82) |
| WMD (95% CI) from E10 | **4.82 (0.86, 8.78)** | **5.02 (1.00, 9.04)** | 0.39 (-3.60, 4.38) | 2.36 (-1.66, 6.40) |

E10 = ezetimibe 10mg; A = atorvastatin; LDL-C = Low density Lipoprotein Cholesterol; HDL-C = High Density Lipoprotein Cholesterol; WMD = weighted mean difference
* same dose, ie, E10 + A10 vs A10; E10 + A20 vs A20; E10 + A40 vs A40; E10 + A80 vs A80
Bolded typography indicates statistically significant differences

The data indicate that a significantly greater per cent of low density lipoprotein cholesterol (LDL-C) and total cholesterol reduction was achieved with concomitant use of ezetimibe and atorvastatin compared with ezetimibe or the corresponding atorvastatin dose taken individually. Increases in high density lipoprotein cholesterol (HDL-C) were not consistently statistically significantly different across the comparisons.

The results of the indirect comparison of co-administration of ezetimibe and atorvastatin versus the ezetimibe/simvastatin FDC are presented below (weighted mean difference (95% CI) for LDL-C, total cholesterol and HDL-C). The submission presented a comparison of atorvastatin:simvastatin 1:2 as atorvastatin was originally recommended for listing by a cost-minimisation approach at this dose relativity.

| **Lipid parameter** | **E10 + A10 versus E/S (10/20)** | **E10 + A20 versus E/S (10/40)** | **E10 + A40 versus E/S (10/80)** |
|---|---|---|---|
| LDL-C | **-8.02 (-14.30, -1.74)** | -5.51 (-11.87, 0.85) | -2.75 (-9.04, 3.54) |
| TC | **-6.61 (-11.45, -1.77)** | **-4.95 (-9.86, -0.04)** | -3.22 (-8.11, 1.67) |
| HDL-C | **-4.82 (-9.46, -0.18)** | **-4.95 (-9.86, -0.04)** | **-5.05 (-10.05, -0.05)** |

E10 = ezetimibe 10mg; A = atorvastatin; E/S = ezetimibe/simvastatin FDC; LDL-C = Low density Lipoprotein Cholesterol; TC = total cholesterol; HDL-C = High Density Lipoprotein Cholesterol
Bolded typography indicates statistically significant differences

The results of Protocol 0692 showed that the co-administration of ezetimibe and atorvastatin provided significant incremental reductions in low density lipoprotein cholesterol (LDL-C) and total cholesterol and increases in high density lipoprotein cholesterol (HDL-C). The pattern of significant incremental reductions in low density lipoprotein cholesterol (LDL-C) and total cholesterol and increases in high density lipoprotein cholesterol (HDL-C) was also observed in Protocol 038 for the ezetimibe/simvastatin FDC. The use of these trials in an indirect comparison is likely to favour atorvastatin as there are differences in the low density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C) changes in the placebo arms of both trials, where Protocol 0692 had statistically significant increases in LDL-C, TC and HDL-C, but Protocol 038 had point

estimate reductions in LDL-C, TC and HDL-C (none of which are statistically significant). These differences in the placebo arms of the trials may indicate that the patients enrolled in the trials were not sufficiently comparable to inform a meaningful indirect comparison. A comparison of ezetimibe + atorvastatin given concomitantly versus the ezetimibe/simvastatin FDC (comparing combinations corresponding to the dose relativity of 1:2 for atorvastatin: simvastatin) demonstrated that the two are non-inferior - although some statistically significant differences are observed, these are unlikely to be clinically significant as the upper confidence intervals are close to one.

The PBAC considered that the indirect comparison suggested non-inferiority of co-administered ezetimibe + atorvastatin versus the ezetimibe/simvastatin FDC, but the comparison was difficult to interpret, and the results seem to depend on the dose of simvastatin.

Overall, no pattern in the reporting of adverse events was observed to suggest increased risk with co-administration of ezetimibe and atorvastatin versus atorvastatin alone in the subjects examined in Protocol 0692. The PBAC noted that the assessment of risk of harm in study P062 was only over 12 weeks. The extended assessment of harms concluded that the longer term safety profile of atorvastatin + ezetimibe co-pack is expected to be no different to that of the components given concomitantly and generally similar to the profile of atorvastatin given alone.

## 9. Clinical Claim

The submission described the ezetimibe + atorvastatin co-pack as equivalent in terms of comparative effectiveness and equivalent in terms of comparative safety over the co-administration of ezetimibe and atorvastatin.

*For PBAC's view see Recommendations and Reasons.*

## 10. Economic Analysis

The submission presented a cost-minimisation analysis, which was based on a non-inferiority claim for LDL-C reduction, not including additional costs/offsets for administration or adverse events.

*For PBAC's view, see Recommendations and Reasons.*

## 11. Estimated PBS Usage and Financial Implications

The estimated total net cost to the PBS was less than $10 million in Year 5.

## 12. Recommendation and Reasons

The PBAC noted that the main comparator nominated in the submission was the corresponding doses of the components (ezetimibe and atorvastatin) given concomitantly, with the ezetimibe/simvastatin fixed dose combination (FDC) as a secondary comparator. The PBAC considered both comparisons were relevant to a consideration of an ezetimibe with atorvastatin combination pack (co-pack).

The PBAC recalled that in 2005 it had recommended simvastatin with ezetimibe (40/10 mg and 80/10 mg) for listing on a cost-minimisation basis compared to the sum of the corresponding strengths (at the price to pharmacist) of the individual components.

The PBAC further recalled that in November 2008, it had advised the Minister under subsection 101(4AC) of the *National Health Act 1953* ('the Act') that the combination item, a fixed dose tablet containing simvastatin with ezetimibe, provided a significant improvement in compliance, for some patients, over the single agents given concomitantly. In July 2009, at the same time as recommending the listing of two new strengths of the FDC simvastatin with ezetimibe product, 10/10 mg and 10/20 mg, the PBAC extended its subsection 101(4AC) advice to include the new strengths.

The PBAC noted that the current application for a co-pack which includes separate tablets of each component. The Committee considered that the evidence presented in November 2008 and July 2009 was not generalizable to this co-pack presentation. The PBAC also noted that the approach for measuring compliance set out in the Compliance to Medicines Working Group Report to the PBAC had not been addressed, and considered that any future submission seeking PBAC advice to the Minister of a compliance benefit relating to the co-pack should address this approach.

The PBAC was also concerned about the labelling and packaging of the co-pack and the risk that the co-pack may not be used correctly by patients, as patients may take only one tablet each day.

The Committee noted that the proposed price of the ezetimibe and atorvastatin co-pack was higher than that for ezetimibe/simvastatin FDC. The Pre Sub Committee Response argued that this is justified on the basis of the PBAC guidelines for the pricing of fixed dose combinations. However, the PBAC noted that it could only recommend a higher price for the ezetimibe and atorvastatin co-pack if it is satisfied that the co-pack provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies. The alternative therapies in this case include the ezetimibe with simvastatin FDC. As the indirect comparison of ezetimibe and atorvastatin given concomitantly versus the ezetimibe/simvastatin FDC (at a ratio of 1:2 for atorvastatin: simvastatin as atorvastatin was originally recommended for listing on cost-minimisation basis at this dose relativity) was inadequate to establish superiority of ezetimibe and atorvastatin over the ezetimibe/simvastatin FDC, the PBAC considered a recommendation to list ezetimibe with atorvastatin at a higher price could not be supported.

Lastly, the PBAC considered that the projected number of prescriptions and the financial impact to Government were underestimated by the submission.

Therefore, the PBAC rejected the application to list the ezetimibe with atorvastatin co-pack on the PBS because of concerns over the labelling and packaging of the co-pack and because the superiority, in terms of comparative efficacy and safety, over the fixed dose combination ezetimibe with simvastatin has not been demonstrated and that the Committee shall not recommend listing if the proposed drug is substantially more costly than the alternative therapy or therapies unless the PBAC is satisfied that, for some patients, it provides a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies.

The PBAC also acknowledged and noted the consumer comments on this item.

***Recommendation***:
**Reject**

## 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 comment.