Public Summary Document

Product: Ezetimibe and Atorvastatin, pack containing 30 tablets ezetimibe 10 mg, and 30 tablets atorvastatin (as calcium) 10 mg, 20 mg, 40 mg or 80 mg, Atozet® Composite Pack
Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd
Date of PBAC Consideration: July 2013

1. Purpose of Application

The resubmission sought an Authority required (Streamlined) listing for hypercholesterolaemia in combination with dietary therapy and exercise where cholesterol levels are inadequately controlled by atorvastatin and patients have hypertension, coronary heart disease (or a family history), diabetes, peripheral vascular disease, heterozygous familial hypercholesterolaemia or cerebrovascular disease.

2. Background

This was the third submission considered by the PBAC. The co-pack of ezetimibe and atorvastatin had been considered previously by the PBAC at the July 2012 meeting and again at the November 2012 meeting. Both submissions sought listing for the treatment, in conjunction with dietary therapy and exercise, of a patient: whose cholesterol levels are inadequately controlled with a HMG CoA reductase inhibitor ('statin') and who meet certain criteria; or who have homozygous familial hypercholesterolaemia.

The PBAC rejected the July 2012 submission because the claim of superiority, in terms of comparative efficacy and safety, over the ezetimibe/simvastatin FDC had not been demonstrated. Further, the PBAC was not satisfied that, for some patients, ezetimibe+atorvastatin would provide a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies.

The PBAC rejected the November 2012 re-submission. No new clinical data were presented, and the claim of improved compliance was withdrawn. A lower price was proposed than in the July 2012 submission. The total cost of listing stated in the submission was less than $10 million over five years.

3. Registration Status

ATOZET® composite pack containing ezetimibe 10 mg and atorvastatin (10, 20, 40 or 80 mg) were TGA registered on 11 February 2013 for the following indications:

- As adjunctive therapy where use of a combination product is appropriate in those patients such as those:
  - not appropriately controlled with atorvastatin or ezetimibe alone; or
  - already treated with atorvastatin and ezetimibe;

- homozygous familial hypercholesterolaemia. Patients may also receive adjunctive treatments (e.g. LDL apheresis).

4. Listing Requested and PBAC's View

Authority required (Streamlined)
Hypercholesterolaemia.

The treatment must be in conjunction with dietary therapy and exercise, AND
Patient must have cholesterol levels that are inadequately controlled with an HMG CoA reductase inhibitor (atorvastatin), AND
Patient must have coronary heart disease OR
Patient must have diabetes mellitus OR
Patient must have peripheral vascular disease OR
Patient must have heterozygous familial hypercholesterolaemia OR
Patient must have symptomatic cerebrovascular disease OR
Patient must have a family history of coronary heart disease OR
Patient must have hypertension.

Inadequate control with atorvastatin is defined as follows:

(1) where the patient falls into a category for which the General Statement for Lipid-Lowering Drugs includes an initial cholesterol threshold for PBS-subsidy (i.e. a patient not in a very high risk category), a cholesterol level in excess of that threshold after at least 3 months of treatment at a maximum tolerated dose of atorvastatin, 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 (i.e. a very high risk category patient), a cholesterol level in excess of 4 mmol per L after at least 3 months of treatment at a maximum tolerated dose of atorvastatin, 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)
Hypercholesterolaemia
Patients must have homozygous familial hypercholesterolaemia, AND
Patients must be eligible for PBS-subsidised lipid lowering medication (according to the criteria set out in the general Statement for Lipid-Lowering Drugs).

For ATOZET Composite Pack 10/10:
Authority required (Streamlined)
Hypercholesterolaemia

Patients must be eligible for PBS-subsidised lipid lowering medication (according to the criteria set out in the general Statement for Lipid-Lowering Drugs), AND

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.

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.

Consistent with the current restriction for the combination of ezetimibe with simvastatin and the current restriction for ezetimibe when co-administered with a HMG CoA reductase inhibitor (statin), the PBAC preferred that "inadequate control" be defined for any HMG CoA reductase inhibitor (statin), not just atorvastatin.

5. Clinical Place for the Proposed Therapy

The sponsor stated that the combination of ezetimibe with atorvastatin would replace the individual components being used together for patients whose cholesterol is inadequately controlled with atorvastatin; or who have homozygous familial hypercholesterolaemia. The PBAC accepted that as this composite pack contained two already listed products, it provides an alternative presentation to the existing options.

6. Comparator

As in previous submissions, the corresponding doses of the components (ezetimibe and atorvastatin) given concomitantly were nominated as the main comparator. The submission also nominated ezetimibe/simvastatin fixed-dose combination (FDC) as a secondary comparator. The PBAC had previously accepted these were the appropriate comparators.

7. Clinical Trials

The trials were the same as the July 2012 submission; there were no new clinical trial data presented in this resubmission.

For further information on the published trials presented in the submission, please refer to the July 2012 PSD at www.pbs.gov.au /info/industry/listing/elements/pbac-meetings/psd/2012-07/ezetimibe-and-atorvastatin

8. Results of Trials

There were no new clinical trial data presented in this resubmission.

For further information on results of trials, please refer to the July 2012 PSD at www.pbs.gov.au /info/industry/listing/elements/pbac-meetings/psd/2012-07/ezetimibe-and-atorvastatin

9. Clinical Claim

The submission claimed that the ezetimibe+atorvastatin co-pack is equivalent in terms of comparative effectiveness and safety over the co-administration of the components; and has similar efficacy and safety with ezetimibe/simvastatin FDC at therapeutically equivalent doses (non-inferiority).

The PBAC accepted the claims.

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/adverse events.

The PBAC noted that the sponsor proposed a price reduction, to equal the sum of the component products at the ex-manufacturer level. The sponsor guaranteed either a discount on the atorvastatin component of ezetimibe+atorvastatin, or the new atorvastatin price as of December 2013 in pricing the co-pack, whichever results in the lowest pricing.

The PBAC noted that the DPMQ of the ezetimibe + atorvastatin co-pack is less expensive than the ezetimibe/simvastatin FDC, and this would result in a net saving to Government when ezetimibe + atorvastatin co-pack replaces the ezetimibe/simvastatin FDC. However, the co-pack is more expensive than ezetimibe and atorvastatin administered concomitantly, and this may result in a net cost to Government when ezetimibe + atorvastatin co-pack replaces the therapies administered concomitantly due to the removal of one average co-payment.

11. Estimated PBS Usage and Financial Implications

The submission presented a market share approach and did not provide an estimation of the number of patients. The submission also estimated total net savings to the PBS of between $10 – 30 million over the first five years.

The PBAC noted that the estimation of the number of scripts was based on underestimated assumptions of market size, market growth, and substitutions away from other therapies (the ezetimibe/simvastatin FDC, and co-administration of rosuvastatin plus ezetimibe). This would likely to underestimate the savings to the Government.

The PBAC also noted that the savings would be accrued from the ezetimibe+atorvastatin co-pack replacing some use of the ezetimibe/simvastatin FDC, which would outweigh the loss of co-payment when the ezetimibe+atorvastatin co-pack replaces its component drugs administered concomitantly.

The financial implications are to be further verified.

12. Recommendation and Reasons

The PBAC recommended an Authority required (Streamlined) listing of ezetimibe and atorvastatin co-pack for hypercholesterolaemia in combination with dietary therapy and exercise where cholesterol levels are inadequately controlled by a statin and patients have hypertension, coronary heart disease (or a family history), diabetes, peripheral vascular disease, heterozygous familial hypercholesterolaemia or cerebrovascular disease, on a cost-minimisation basis with the corresponding doses of the components (ezetimibe and atorvastatin) given concomitantly.

However, the PBAC remained of the view that there was no compelling clinical need for the co-pack product, and remained concerned that it might direct use inappropriate from adequate titration of statins given alone.

The PBAC had previously accepted the corresponding doses of the components (ezetimibe and atorvastatin) given concomitantly, as well as ezetimibe/simvastatin fixed-dose combination (FDC) were the appropriate comparators.

The PBAC accepted the claim that the ezetimibe+atorvastatin co-pack is equivalent in terms of comparative effectiveness and safety with the co-administration of the components; and has similar efficacy and safety to ezetimibe/simvastatin FDC at therapeutically equivalent doses (non-inferiority).

The PBAC noted a price reduction was offered. The sponsor guaranteed either a discount on the atorvastatin component of ezetimibe+atorvastatin, or the atorvastatin component of ezetimibe+atorvastatin will be reduced to reflect the new atorvastatin price.

The PBAC recalled that at its November 2008 meeting, it advised the Minister under subsection 101(4AC) of the *National Health Act 1953* and the Pharmaceutical Benefits Pricing Authority (PBPA) that ezetimibe and simvastatin FDC had a significant improvement in compliance over its alternative therapies for some patients, at the time of listing, was ezetimibe administered concomitantly with simvastatin. The PBAC recalled also that this advice was given before the finalisation of the Compliance to Medicines Working Group report, and that the criteria of that report had therefore not been used to assess the compliance claims for that product as they have for all compliance claims since.

The PBAC considered that the impending PBS listing of ezetimibe and atorvastatin co-pack would allow the co-pack to be considered as an alternative therapy to the ezetimibe and simvastatin FDC. The PBAC therefore considered that the basis of its previous advice to the Minister under subsection 101(4AC) for the ezetimibe and simvastatin FDC will need to be reviewed, given that the new alternative therapy will be available.

The PBAC therefore invited the sponsor of the ezetimibe and simvastatin FDC to submit data in support of its continued claim of compliance benefit and that any future submission seeking PBAC advice to the Minister of a compliance benefit would need to address the approach for measuring compliance set out in the Compliance to Medicines Working Group Report to the PBAC.

The PBAC noted that the sponsor of ezetimibe and atorvastatin had withdrawn its claims of compliance benefit under subsection 101(4AC) of the *National Health Act 1953* from its second submission in November 2012.

The PBAC recommended, under section 101 (3BA) of the *National Health Act*, that ezetimibe and atorvastatin co-pack should be treated as interchangeable on an individual patient basis with ezetimibe and simvastatin FDC.

The PBAC considered that ezetimibe and atorvastatin co-pack is suitable for inclusion in the list of medicines for prescribing by nurse practitioners within collaborative arrangements as continuing therapy only.

Outcome:
Recommended

Recommended listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
EZETIMIBE AND ATORVASTATIN				
Pack containing 30 tablets ezetimibe 10 mg and 30 tablets atorvastatin 10 mg (as calcium)	60	5	Atozet	MK
Pack containing 30 tablets ezetimibe 10 mg and 30 tablets atorvastatin 20 mg (as calcium)	60	5	Atozet	MK
Pack containing 30 tablets ezetimibe 10 mg and 30 tablets atorvastatin 40 mg (as calcium)	60	5	Atozet	MK
Pack containing 30 tablets ezetimibe 10 mg and 30 tablets atorvastatin 80 mg (as calcium)	60	5	Atozet	MK

The following indication of 'hypercholesterolaemia' will be repeated seven times (to reflect the 7 different Streamlined Authority codes) in the Schedule, with the only difference being the requirement for the patient to have one of the following co-morbidities: coronary heart disease, diabetes mellitus, peripheral vascular disease, heterozygous familial hypercholesterolaemia, symptomatic cerebrovascular disease, family history of coronary heart disease or hypertension.

Condition/Indication:	Hypercholesterolaemia
Restriction:	Authority required (STREAMLINED)

Clinical criteria:	The treatment must be in conjunction with dietary therapy and exercise, AND The condition must be inadequately controlled with an HMG CoA reductase inhibitor AND Patient must have coronary heart disease OR Patient must have diabetes mellitus OR Patient must have peripheral vascular disease OR Patient must have heterozygous familial hypercholesterolaemia OR Patient must have symptomatic cerebrovascular disease OR Patient must have a family history of coronary heart disease OR Patient must have hypertension.
Definitions	Inadequate control with a statin is defined as follows: (1) where the patient falls into a category for which the General Statement for Lipid-Lowering Drugs includes an initial cholesterol threshold for PBS-subsidy (i.e. a patient not in a very high risk category), a cholesterol level in excess of that threshold after at least 3 months of treatment at a maximum tolerated dose of a statin, in conjunction with dietary therapy and exercise. The dose and duration of the 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 (i.e. a very high risk category patient), a cholesterol level in excess of 4 mmol per L after at least 3 months of treatment at a maximum tolerated dose of a statin, in conjunction with dietary therapy and exercise. The dose and duration of the statin treatment and the cholesterol level which shows inadequate control must be documented in the patient's medical records when ezetimibe is initiated.
Administrative advice	Note Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for nurse Practitioners.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
EZETIMIBE AND ATORVASTATIN			
Pack containing 30 tablets ezetimibe 10 mg and 30 tablets atorvastatin 10 mg (as calcium)	60	5	Atozet MK
Pack containing 30 tablets ezetimibe 10 mg and 30 tablets atorvastatin 20 mg (as calcium)	60	5	Atozet MK
Pack containing 30 tablets ezetimibe 10 mg and 30 tablets atorvastatin 40 mg (as calcium)	60	5	Atozet MK
Pack containing 30 tablets ezetimibe 10 mg and 30 tablets atorvastatin 80 mg (as calcium)	60	5	Atozet MK

Condition/Indication:	Hypercholesterolaemia
Restriction:	Authority required (STREAMLINED)
Treatment criteria:	Hypercholesterolaemia.
Clinical criteria:	Patients must be eligible for PBS-subsidised lipid lowering medication according to the criteria set out in the general Statement for Lipid-Lowering Drugs, AND The condition must be homozygous familial hypercholesterolaemia.
Administrative advice	Note Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for nurse Practitioners.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
EZETIMIBE AND ATORVASTATIN			
Pack containing 30 tablets ezetimibe 10 mg and 30 tablets atorvastatin 10 mg (as calcium)	60	5	Atozet MK

Condition/Indication:	Hypercholesterolaemia
Restriction:	Authority required (STREAMLINED)
Clinical criteria:	Patient must be eligible for PBS-subsidised lipid lowering medication according to the criteria set out in the general Statement for Lipid-Lowering Drugs. AND 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 *atorva*statin dose.
Prescriber instructions:	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.
Administrative advice	Note Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for nurse Practitioners.

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 welcomes the recommendation from the PBAC and considers that there is a high clinical need for a composite pack.

The sponsor considers that interchangeability between ATOZET and VYTORIN is inconsistent with previous PBAC decisions and not warranted given that simvastatin and atorvastatin were in separate therapeutic groups.