5.4 EZETIMIBE + ATORVASTATIN fixed dose combination tablets; 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg; Atozet®; Merck Sharp & Dohme (Australia) Pty Ltd.

1 Purpose of Application

1.1 The major submission sought an Authority Required (STREAMLINED) listing for the treatment of hypercholesterolaemia in patients who meet certain criteria. The fixed dose combination (FDC) tablets were intended to replace the existing composite packs.

2 Requested listing

2.1 As the FDC tablets were intended to replace the composite packs, the same listing as the existing composite packs was sought.

3 Background

3.1 The FDC was considered under the TGA/PBAC parallel process and was considered at the October 2014 Advisory Committee on Prescription Medicines (ACPM) meeting. In addition to the clinical evaluation report that was available during the evaluation, a positive delegate's summary was provided in September 2014. The positive ACPM resolution from October 2014 was provided with the Pre-PBAC response.

3.2 The PBAC has not previously considered the requested dosage form although the FDC was submitted for consideration in July 2012, but withdrawn prior to the PBAC meeting. In July 2013 the PBAC recommended the ezetimibe + atorvastatin co-pack.

4 Clinical place for the proposed therapy

4.1 The submission indicated that the ezetimibe/atorvastatin FDC will have the same clinical place in therapy as the co-pack, replacing the individual components used together for patients whose cholesterol is inadequately controlled with a statin or who have homozygous familial hypercholesterolaemia.

5 Comparator

5.1 The submission nominated ezetimibe + atorvastatin co-pack as well as the individual components used concomitantly as the main comparator. These were considered appropriate comparators by the Commentary. Ezetimibe/simvastatin FDC was included as a secondary comparator for the co-pack, which was accepted by the PBAC and is also relevant here.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission presented two bioequivalence trials (P391 and P392), which were submitted to the TGA as part of the registration dossier.

Trials presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Bioequivalence trials		
P391	A Single-Dose, Full Replicate, Comparative Bioavailability Study of Two Formulations of Ezetimibe/Atorvastatin Calcium 10 mg/10 mg FDC Tablets vs. Ezetrol® administered with Lipitor® under Fasting Conditions	Not published
P392	A Single-Dose, Full Replicate, Comparative Bioavailability Study of Two Formulations of Ezetimibe/Atorvastatin Calcium 10 mg/80 mg FDC Tablets vs. Ezetrol® administered with Lipitor® under Fasting Conditions	Not published

Source: Table B.2.2, p.21 of the submission

Clinical claim

6.4 The submission claimed that ezetimibe/atorvastatin FDC is equivalent to the co-administration of its components in terms of comparative effectiveness and safety. The PBAC accepted this claim for the co-pack in July 2013 (paragraphs 6.4 and 6.5, July 2013 PBAC Minutes). The submission also claimed that the ezetimibe/atorvastatin FDC is bioequivalent to co-administration of corresponding doses of ezetimibe and atorvastatin for all tested pharmacokinetic parameters.

6.5 The submission claimed non-inferior comparative effectiveness and non-inferior comparative safety of ezetimibe + atorvastatin FDC compared with ezetimibe + atorvastatin co-pack.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Economic analysis

6.6 The submission presented a cost-minimisation analysis, assuming the ezetimibe/atorvastatin FDC is equi-effective to the corresponding doses of the individual components given concomitantly.

6.7 The requested ex-manufacturer price of ezetimibe/atorvastatin FDC was based on the sum of atorvastatin and ezetimibe prices. This pricing method was previously accepted by the PBAC for the calculation of the co-pack price in July 2013. The requested price of ezetimibe/atorvastatin FDC is shown in the table below.

Proposed PBS price for ezetimibe/atorvastatin FDC

Ezetimibe/atorvastatin FDC	Atorvastatin	Ezetimibe	Ex-man	DPMQ
10mg/10mg	$9.30	$54.58	$63.88	$82.18
10mg/20mg	$13.72	$54.58	$68.30	$87.41
10mg/40mg	$19.32	$54.58	$73.90	$94.04
10mg/80mg	$27.62	$54.58	$82.20	$103.85

Source: Table A.2.1, p4 of the submission

6.8 In the July 2013 co-pack resubmission, the sponsor guaranteed either a [redacted] discount on the atorvastatin component, or if the price disclosure reduction was greater than [redacted], the price of the atorvastatin component would be reduced to reflect the new price (paragraph 6.7, July 2013 PBAC Minutes). Given that atorvastatin is included in the 1 October 2014 price disclosure cycle, the price of the FDC would have needed to be recalculated.

6.9 Although not a matter for the PBAC, these listings will create new brands of pharmaceutical items containing the drug "atorvastatin and ezetimibe". Ezetimibe has not yet been subject to a 16% (or 12.5%) statutory price reduction under Division 3A of the *National Health Act* 1953. The submission uses the current prices of ezetimibe and the price of the FDC would need to be recalculated to take into account a 16% price reduction to the ezetimibe component. The PSCR (p2) stated that no statutory price reduction should occur.

6.10 In July 2013, the PBAC advised the Minister that the combination drug ezetimibe+atorvastatin (co-pack) should be treated as interchangeable on an individual patient basis with the combination drug ezetimibe/simvastatin FDC, and in November 2013 the combination drug ezetimibe+rosuvastatin (co-pack) was also considered interchangeable. This advice applies to the combination drug ezetimibe+atorvastatin regardless of the form (co-pack or FDC).

6.11 In March 2014, a minor submission requested that the PBAC reconsider its recommendation that atorvastatin+ezetimibe co-pack should be treated as interchangeable with simvastatin/ezetimibe FDC. The PBAC considered that the submission did not provide evidence to support the claim that atorvastatin+ezetimibe is superior to simvastatin/ezetimibe. The PBAC therefore rejected the submission, reaffirming its recommendation from July 2013 that the two products should be treated as interchangeable.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Drug cost/patient/year: $986.16 (at 10 mg/10 mg daily) - $1,246.20 (at 10 mg/80 mg daily)

6.12 The cost of ezetimibe/atorvastatin FDC per patient per year varies from $986.16 at the lowest recommended dosage to $1,246.20 per patient per year at the highest daily dose. Treatment is on-going.

Estimated PBS usage & financial implications

6.13 This submission was not considered by DUSC. The submission used a market share approach applying the same methodology as used in the July 2013 resubmission for the co-pack. While the methodology remained the same between the two submissions, the uptake rates were changed in the current FDC submission – increased for uptake from atorvastatin monotherapy and decreased for uptake from concomitant ezetimibe and atorvastatin. The change in uptake had a considerable impact on the number of scripts and therefore estimated savings, increasing both (see table below for estimates).

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scripts July 2013 co-pack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated changes in cost of listing ezetimibe/atorvastatin FDC					
Net cost for FDC listing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost of items replaced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated total net cost					
Estimated savings	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated savings July 2013 co-pack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Excel workbook 'Appendix 10 Usage and Financial Estimates.xlsx' provided with the submission

Estimated financial impact: Savings of less than $10 million per year in Year 1, increasing to a saving of less than $10 million per year in Year 5.

6.14 The submission estimated a cumulative net saving over five years to the PBS of $25.3 million. This is $6.5M more than the estimated savings of $18.8M in the July 2013 co-pack resubmission. Whether these additional savings will be realised depends on whether the submission's revised uptake estimates are accurate. The PSCR (p1) argued that this is reasonable due to clinician and patient preference for FDCs.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Quality Use of Medicines

6.15 In relation to the ezetimibe + atorvastatin co-pack, in July 2013 the PBAC commented that there was no compelling clinical need for the co-pack product, and was concerned that it might direct use away from adequate titration of statins given alone. These concerns remained relevant to the FDC.

7 PBAC Outcome

7.1 The PBAC recommended listing the FDC tablets for the same Authority Required (STREAMLINED) listings as applied to the existing composite packs, on a cost-minimisation basis with the individual components taken concomitantly.

7.2 The PBAC was satisfied that ezetimibe + atorvastatin FDC is equivalent to the ezetimibe + atorvastatin co-pack in terms of efficacy and safety and should be priced the same.

7.3 The PBAC considered that the additional savings claimed in the submission from the increased use of FDCs over co-packs due to clinician and patient preference were doubtful.

7.4 In November 2013, the PBAC noted that in contrast to the statins, there are no patient relevant outcome data for ezetimibe. However, the largest contribution to the price of the combination is from the ezetimibe component. The PBAC reiterated its view that the Minister may wish to consider requesting the PBAC to undertake a review of, and subsequently provide advice to the Minister regarding, the cost-effectiveness of ezetimibe, taking into account the latest available evidence and best practice.

7.5 The PBAC advised that ezetimibe + atorvastatin FDC is suitable for inclusion in the list of medicines for prescribing by nurse practitioners within collaborative arrangements as continuing therapy only.

7.6 The PBAC recommended that the Safety Net 20 Day Rule should apply.

7.7 Advice to the Minister under section 101 3BA of the *National Health Act*
In accordance with subsection 101(3BA) of the *National Health Act* 1953, the PBAC advised that it is of the opinion that ezetimibe + atorvastatin should be treated as interchangeable on an individual patient basis with ezetimibe + rosuvastatin, and with ezetimibe + simvastatin.

7.8 The PBAC was not satisfied as required by section 101(4AC) of the *National Health Act* 1953 that atorvastatin with ezetimibe, fixed dose combination tablets, provides for some patients, a significant improvement in compliance, or, a significant improvement in efficacy or reduction in toxicity over alternative therapy and therefore will not provide advice to the Minister under that section. The PBAC considered that the submission's claim of potentially improved compliance through a reduction in costs (i.e. through reduced co-payments) and reduced pill burden dosing complexity with the proposed new therapy would apply equally to alternative therapies that are also fixed dose combination tablets and that any claim under this section of the Act should be made in the context of Section C3 of the Compliance to Medicines Working Group Report to PBAC, April 2010.

Outcome:
Recommended

8 Recommended listing

8.1 Add the following new items:

Name, Restriction, Manner of administration and form	Max. Qty (Packs)	№.of Rpts	Proprietary Name and Manufacturer	
ATORVASTATIN + EZETIMIBE				
atorvastatin 10 mg + ezetimibe 10 mg tablets, 30	1	5	Atozet®	MK
atorvastatin 20 mg + ezetimibe 10 mg tablets, 30	1	5	Atozet®	MK
atorvastatin 40 mg + ezetimibe 10 mg tablets, 30	1	5	Atozet®	MK
atorvastatin 80 mg + ezetimibe 10 mg tablets, 30	1	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 specified co-morbidities (marked with *):*

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	---
Severity:	---
Condition:	Hypercholesterolaemia
PBS Indication:	Hypercholesterolaemia ***(4068, 4085, 4086, 4069, 4120, 4121)***
Treatment phase:	---
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	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 (statin) AND *Patient must have coronary heart disease ***(4068)*** *Patient must have diabetes mellitus ***(4085)*** *Patient must have peripheral vascular disease ***(4086)*** *Patient must have heterozygous familial hypercholesterolaemia ***(4069)*** *Patient must have symptomatic cerebrovascular disease ***(4096)*** *Patient must have a family history of coronary heart disease ***(4120)*** *Patient must have hypertension ***(4121)***

Prescriber Instructions	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 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 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.
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.

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	---
Severity:	---
Condition:	Hypercholesterolaemia
PBS Indication:	Hypercholesterolaemia ***(4097)***
Treatment phase:	---
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	Patient must have homozygous familial hypercholesterolaemia AND Patient must be eligible for PBS-subsidised lipid lowering medication according to the criteria set out in the general Statement for Lipid-Lowering Drugs

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 (Packs)	№.of Rpts	Proprietary Name and Manufacturer
ATORVASTATIN (&) EZETIMIBE atorvastatin 10mg + ezetimibe 10 mg tablets, 30	1	5	Atozet® MK

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	---
Severity:	---
Condition:	Hypercholesterolaemia
PBS Indication:	Hypercholesterolaemia ***(4353)***
Treatment phase:	---
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒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 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.

9 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.

10 Sponsor's Comment

The sponsor had no comment.