

**5.6 EZETIMIBE + ROSUVASTATIN, tablets,
ezetimibe 10mg + rosuvastatin 5mg; ezetimibe 10mg +
rosuvastatin 10mg; ezetimibe 10mg + rosuvastatin 20mg;
ezetimibe 10mg + rosuvastatin 40mg,
Rosuzet[®], Merck Sharp & Dohme Australia Pty Ltd**

1 Purpose of Application

1.1 To seek an Authority Required (STREAMLINED) listing for treatment of hypercholesterolaemia in a patient who meets certain criteria.

2 Requested listing

2.1 The submission sought the following listing:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
EZETIMIBE AND ROSUVASTATIN				
Tablet 10mg/5mg				
Tablet 10mg/10mg	30	5	Rosuzet [®]	MK
Tablet 10mg/20mg	30	5	Rosuzet [®]	MK
Tablet 10mg/40mg	30	5	Rosuzet [®]	MK
	30	5	Rosuzet [®]	MK

Authority required (STREAMLINED)

Hypercholesterolaemia.

The clinical criteria is:

The treatment must be in conjunction with dietary therapy and exercise,

AND the clinical criteria is:

Patient must have cholesterol levels that are inadequately controlled with rosuvastatin,

AND the clinical criteria is:

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 rosuvastatin 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 rosuvastatin, in conjunction with dietary therapy and exercise. The dose and duration of rosuvastatin 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 rosuvastatin 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 rosuvastatin, in conjunction with dietary therapy and exercise. The dose and duration of rosuvastatin 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

The clinical criteria is :

Patients must have homozygous familial hypercholesterolaemia,

AND the clinical criteria is:

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

Authority required (STREAMLINED)

Hypercholesterolaemia

The clinical criteria is:

Patients must be eligible for PBS-subsidised lipid lowering medication

AND the clinical criteria is:

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:

- (1) Severe myalgia (muscle symptoms without creatine kinase elevation) which is proved to be temporally associated with statin treatment; or
- (2) 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
- (3) Unexplained, persistent elevations of serum transaminases (greater than 3 times the upper limit of normal) during treatment with a statin.

- 2.2 Listing was sought on a cost-minimisation basis with the price requested being less than the sum of the individual components and the same as the price at which the ezetimibe + rosuvastatin co-pack was recommended.

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

3 Background

- 3.1 This application is being processed under the TGA/PBAC parallel process. A positive Delegate's Overview was received on 1 July 2014 and is expected to be considered by the Advisory Committee on Prescription Medicines (ACPM) in August 2014.
- 3.2 In November 2013, the PBAC recommended the ezetimibe + rosuvastatin co-pack. The sponsor has not proceeded with this listing.
- 3.3 In November 2013, the PBAC advised the Minister that the combination drug ezetimibe + rosuvastatin co-pack should be treated as interchangeable on an individual patient basis with the ezetimibe + atorvastatin co-pack and the ezetimibe + simvastatin FDC. The PBAC reaffirmed this advice as applicable to the combination drug ezetimibe + rosuvastatin regardless of the form (co-pack or FDC).
- 3.4 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, however the PBAC considered that the submission did not provide evidence to support a claim of superiority over ezetimibe + simvastatin and the submission was rejected.

4 Clinical place for the proposed therapy

- 4.1 The submission stated that the ezetimibe + rosuvastatin 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 rosuvastatin or who have homozygous familial hypercholesterolaemia.
- 4.2 In November 2013, the PBAC considered that the ezetimibe + rosuvastatin co-pack would also replace the ezetimibe + atorvastatin co-pack and ezetimibe + simvastatin FDC.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

5 Comparator

- 5.1 The submission nominated ezetimibe and rosuvastatin co-pack as the main comparator, as well as the individual components used concomitantly.
- 5.2 In consideration of the ezetimibe + rosuvastatin co-pack, the PBAC considered that the ezetimibe + atorvastatin co-pack and ezetimibe + simvastatin FDC were also relevant comparators.

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 This submission does not present any new clinical or economic information in addition to what PBAC has seen previously, other than bioequivalence data submitted to the TGA for registration of the FDC.
- 6.4

Trial ID	Publication details	Publication citation
Direct randomised trial(s)		

Protocol 417 MK-0653H 417-00	A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of fixed dose combination of rosuvastatin calcium + ezetimibe 40/10 mg tablets of Sun Pharmaceutical Industries Ltd., India and co-administration of Crestor® (rosuvastatin calcium) 40mg tablet of AstraZeneca with Ezetrol® (ezetimibe) 10 mg tablets of Merck Sharp & Dohme, in 60 healthy human adult subjects, under fasting conditions.	Not published
Protocol 425 MK 0653H 425-00	A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of fixed dose combination of rosuvastatin calcium + ezetimibe 5/10 mg tablets of Sun Pharmaceutical Industries Ltd., India and co-administration of Crestor® (rosuvastatin calcium) 5mg tablet of AstraZeneca with Ezetrol® (ezetimibe) 10 mg tablets of Merck Sharp & Dohme, in 60 healthy human adult subjects, under fasting conditions.	Not published

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

Clinical claim

- 6.5 The clinical claim in the submission is the same as that accepted by the PBAC in November 2013 for the co-pack.
- 6.6 The clinical claim is that the ezetimibe + rosuvastatin FDC is equivalent in terms of comparative effectiveness and safety to the co-administration of the individual components; and has similar efficacy and safety to ezetimibe + simvastatin FDC at therapeutically equivalent doses.
- 6.7 The PBAC again noted no claim was made with respect to a comparison with the combination drug atorvastatin with ezetimibe.
- 6.8 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 6.9 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 6.10 The submission proposed that the price be calculated based on the atorvastatin + ezetimibe combination product at the ex-manufacturer level, incorporating a relativity between rosuvastatin and atorvastatin of 1:2.2.
- 6.11 In consideration of the ezetimibe + rosuvastatin co-pack, the PBAC considered this approach was appropriate based on the approved ex-manufacturer prices of the two drugs in November 2013.

Atorvastatin dose	Ex-man	\$/mg	Rosuvastatin dose	Ex-man	Relativity
10	\$9.30	\$0.031	5	\$10.23	2.2
20	\$13.72	\$0.023	10	\$15.09	2.2
40	\$19.32	\$0.016	20	\$21.25	2.2
80	\$27.62	\$0.012	40	\$30.38	2.2

- 6.12 The PBAC noted that both atorvastatin and rosuvastatin are included in the first cycle of simplified price disclosure and will be required to reduce their prices on 1 October 2014. Therefore the price of the combination will need to be recalculated.
- 6.13 The submission stated that ezetimibe + rosuvastatin should not be treated as interchangeable with ezetimibe + simvastatin FDC because the individual statin

components (simvastatin and rosuvastatin) were placed in two distinct therapeutic groups.

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

Estimated PBS usage & financial implications

- 6.14 The submission's derived estimates of use are the same as for the ezetimibe + rosuvastatin co-pack submission.
- 6.15 The PBAC noted that the two submissions (FDC and co-pack) counted the same savings, and considered that this was inappropriate as both sets of savings cannot be realised.
- 6.16 Given that the co-pack has already been recommended by the PBAC, the net cost to the PBS of listing the FDC would be expected to be nil as there is no change to the agreed price, quantity, utilisation or restriction for the FDC compared to that already agreed for the co-pack.

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

7 PBAC Outcome

- 7.1 The PBAC recommended an Authority Required (Streamlined) listing of ezetimibe + rosuvastatin FDC 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.
- 7.2 The PBAC noted that the listing should be consistent with the recommended listing for the ezetimibe + rosuvastatin co-pack.
- 7.3 The PBAC is satisfied that ezetimibe + rosuvastatin FDC is equivalent to the ezetimibe + rosuvastatin co-pack in terms of efficacy and safety and should be priced the same.
- 7.4 The Committee accepted the relativity of rosuvastatin:atorvastatin of 1:2.2 and agreed that the price of the FDC should be the same as the price for the co-pack, noting that the co-pack listing has not proceeded and the price will now need to be recalculated as a result of price disclosure.
- 7.5 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.
- 7.6 The PBAC advised that ezetimibe + rosuvastatin FDC is suitable for inclusion in the list of medicines for prescribing by nurse practitioners within collaborative arrangements as continuing therapy only.
- 7.7 The PBAC recommended that the Safety Net 20 Day Rule should apply.

- 7.8 Advice to the Minister under Subsection 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 + rosuvastatin should be treated as interchangeable on an individual patient basis with ezetimibe + atorvastatin, and with ezetimibe and simvastatin.

Outcome:
 Recommended.

8 Recommended listing

- 8.1 Add the following new items:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
EZETIMIBE AND ROSUVASTATIN				
ezetimibe 10mg + rosuvastatin 5mg tablets, 30	1	5	Rosuzet®	MK
ezetimibe 10mg + rosuvastatin 10mg tablets, 30	1	5	Rosuzet®	MK
ezetimibe 10mg + rosuvastatin 20mg tablets, 30	1	5	Rosuzet®	MK
ezetimibe 10mg + rosuvastatin 40mg tablets, 30	1	5	Rosuzet®	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 *):*

Condition:	Hypercholesterolaemia
Restriction:	Authority required (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 *Patient must have diabetes mellitus *Patient must have peripheral vascular disease *Patient must have heterozygous familial hypercholesterolaemia *Patient must have symptomatic cerebrovascular disease *Patient must have a family history of coronary heart disease *Patient must have hypertension.

Prescriber Instructions	<p>Inadequate control with a statin is defined as follows:</p> <p>(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</p> <p>(2) where the patient falls into a category for which the General Statement for Lipid-Lowering Drugs allows PBS-subsidised treatment with a <i>statin</i> 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 <i>statin</i>, in conjunction with dietary therapy and exercise. The dose and duration of <i>statin</i> 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.</p>
Administrative Advice	<p><u>Note</u></p> <p>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.</p>

Condition:	Hypercholesterolaemia
Restriction:	Authority required (STREAMLINED)
Clinical criteria:	<p>Patient must have homozygous familial hypercholesterolaemia</p> <p>AND</p> <p>Patient must be eligible for PBS-subsidised lipid lowering medication according to the criteria set out in the general Statement for Lipid-Lowering Drugs</p>
Administrative advice	<p><u>Note</u></p> <p>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.</p>

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
EZETIMIBE AND ROSUVASTATIN ezetimibe10mg + rosuvastatin 5mg tablets, 30	1	5	Rosuzet MK

Condition:	Hypercholesterolaemia
Restriction:	Authority required (STREAMLINED)
Clinical criteria:	<p>Patient must be eligible for PBS-subsidised lipid lowering medication according to the criteria set out in the general Statement for Lipid-Lowering Drugs.</p> <p>AND</p> <p>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.</p>
Prescriber instructions:	<p>A clinically important product-related adverse event is defined as follows:</p> <p>(i) Severe myalgia (muscle symptoms without creatine kinase elevation) which is proven to be temporally associated with statin treatment; or</p> <p>(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</p> <p>(iii) Unexplained, persistent elevations of serum transaminases (greater than 3 times the upper limit of normal) during treatment with a statin.</p>
Administrative advice	<p><u>Note</u></p> <p>Continuing Therapy Only:</p> <p>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.</p>

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.