PUBLIC SUMMARY DOCUMENT

Product: Ezetimibe and rosuvastatin, pack containing 30 tablets ezetimibe 10 mg, and 30 tablets rosuvastatin 5 mg, 10 mg, 20 mg or 40 mg, Rosuzet® Composite Pack
Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd.
Date of PBAC Consideration: November 2013

1. Purpose of Application

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

This application was processed under the TGA/PBAC parallel process. The PBAC noted that the Advisory Committee on Prescription Medicines (ACPM) had recommended approval of the co-pack.

2. Background

The PBAC had not previously considered this co-pack.

Listing of a similar co-pack containing ezetimibe and atorvastatin was recommended by the PBAC at their July 2013 meeting. The Public Summary Document is available on the PBS Website.

3. Registration Status

Ezetimibe and atorvastatin composite pack was TGA registered on the 26 November 2013 for:

- Primary Hypercholesterolaemia:- as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia where use of a combination product is appropriate in those patients:
  - not appropriately controlled with rosuvastatin or ezetimibe alone; or
  - already treated with rosuvastatin and ezetimibe.
- Homozygous Familial Hypercholesterolaemia (HoFH): Patients may also receive adjunctive treatments (e.g., LDL apheresis).

4. Listing Requested and PBAC's View

Listing was requested on a cost-minimisation basis with the individual components included in the co-pack (ie. ezetimibe and rosuvastatin).

Authority Required (STREAMLINED) (ROSUZET Composite Pack 10/5, 10/10, 10/20, and 10/40)

Hypercholesterolaemia.

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

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) (ROSUZET Composite Pack 10/5, 10/10, 10/20, and 10/40)
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).

Consistent with the recommended restriction for the atorvastatin + ezetimibe co-pack, 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 rosuvastatin.

5. Clinical Place for the Proposed Therapy

The submission stated that the combination of ezetimibe with rosuvastatin (co-pack) would replace the individual components being used together for patients whose cholesterol is inadequately controlled with rosuvastatin or who have homozygous familial hypercholesterolaemia.

6. Comparator

The submission nominated ezetimibe + rosuvastatin (concomitant), as the main comparator and ezetimibe+simvastatin fixed dose combination (FDC) (VYTORIN) as a secondary comparator.

The PBAC agreed with the commentary and Economic Sub-Committee (ESC) that the combination drug atorvastatin + ezetimibe (co-pack), recommended at the July 2013 PBAC meeting was also a relevant comparator.

The PBAC noted that rosuvastatin and atorvastatin are considered the higher potency statins (compared to simvastatin and pravastatin). The atorvastatin+ezetimibe co pack is therefore an appropriate comparator from a pharmacological analogue perspective. The PBAC also noted that a multiple comparator approach was consistent with previous considerations of atorvastatin+ezetimibe (co pack).

Therefore, the PBAC considered that the therapies that prescribers would most replace in practice are ezetimibe + rosuvastatin (concomitant), ezetimibe+simvastatin fixed dose combination (FDC) and atorvastatin+ezetimibe (co-pack).

7. Clinical Trials

The submission presented:

- Two randomised trials (EXPLORER trial and Protocol P03317) which both compare concomitant ezetimibe and rosuvastatin to rosuvastatin monotherapy.

- An indirect comparison of ezetimibe + rosuvastatin (concomitant) versus the ezetimibe+simvastatin (FDC), using rosuvastatin 40mg as the common reference.

- Proof of registration and confirmation of the bioequivalence of the generic Merck Sharp & Dohme (MSD) rosuvastatin used in the composite pack. with the originator product (Crestor®)

The trials and associated reports presented in the submission for the comparison of ezetimibe +rosuvastatin (concomitant) versus the therapies given individually are shown in the following table.

Trials and associated reports presented in the submission

Trial	Protocol title	Publication citation
P03317	PROTOCOL 03317: SCH 58235: ASSESSMENT OF A MULTIPLE-DOSE DRUG INTERACTION BETWEEN EZETIMIBE AND ROSUVASTATIN IN HEALTHY HYPERCHOLESTEROLEMIC SUBJECTS	Pharmacodynamic interaction between ezetimibe and rosuvastatin. Kosoglou T, Statkevich P, Yang B, Suresh R, Zhu Y, Boutros T et al. Curr Med Res Opin 2004; 20(8):1185-1195.

EXPLORER Study	Efficacy and safety of Rosuvastatin 40mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study).	Ballantyne CM, Weiss R, Moccetti T, Vogt A, Eber B, Sosef F, Duffield E. The American journal of Cardiology 2007; 99:673-680.

The trials and associated reports presented in the submission for the indirect comparison of co-administered ezetimibe and rosuvastatin versus the ezetimibe/simvastatin FDC (Vytorin®) are shown in the following table.

Trials and associated reports presented in the submission

Trial	Publication title	Publication citation
P058	Lipid-altering efficacy of the ezetimibe/simvastatin single tablet versus rosuvastatin in hypercholesterolemic patients.	Catapano AL, Davidson MH, Ballantyne CM, Brady WE, Gazzara RA, Tomassini JE, Tershakovec AM. Current Medical Research and Opinion Vol 22, No 10, 2006, 2041-2053.
EXPLORER Study	As above	As above

8. Results of Trials

With regard to comparative effectiveness, the PBAC recalled that the efficacy of rosuvastatin in combination with ezetimibe for the treatment of hypercholesterolemia had previously been accepted on the basis of the EXPLORER trial.

The results of the indirect comparison of ezetimibe + rosuvastatin (concomitant) versus ezetimibe + simvastatin (FDC) showed a significantly higher reduction in LDL-C and total cholesterol with the ezetimibe+rosuvastatin 40 mg co-pack over each of the three ezetimibe+simvastatin FDCs.

The PBAC noted that this is consistent with the 'Review of Statin Therapies' considered by PBAC at its July 2012 meeting, that reaffirmed the PBAC's previous recommendation that rosuvastatin is more effective than simvastatin. However, the results of the indirect comparison are biased toward rosuvastatin because the therapeutic relativities between the statin components used (rosuvastatin: simvastatin; 2:1, 1:1 and 1:2) are lower than the relativity claimed by the submission (rosuvastatin: simvastatin; 1:6).

With regard to comparative harms, overall, no pattern in the reporting of adverse events suggested increased risk with co-administration of ezetimibe and rosuvastatin versus rosuvastatin alone in the subjects examined in EXPLORER and Protocol P03317. The PBAC recalled that they had previously noted that no significant toxicity signals had emerged with use of ezetimibe co administered with rosuvastatin, based on the data from EXPLORER trial (ezetimibe submission, November 2010 PSD available here).

9. Clinical Claim

The submission claimed that the ezetimibe+rosuvastatin co-pack is equivalent in terms of comparative effectiveness and safety over the co-administration of the components.

The submission claimed that the ezetimibe+rosuvastatin co-pack is equi-effective to ezetimibe + simvastatin FDC based on a therapeutic relativity of 1:6.

The PBAC accepted these claims. The Committee noted no claim was made with respect to a comparison with the combination drug atorvastatin with ezetimibe.

10. Economic Analysis

The submission presented a cost-minimisation analysis with the price requested for the ezetimibe + rosuvastatin (co-pack) being the sum of the component products (at ex-manufacturer prices).

The PBAC noted that a reduced price was proposed in the sponsor's pre-PBAC Response, such that the price of ezetimibe+rosuvastatin (co-pack) was claimed to be no higher than that of the ezetimibe + atorvastatin co-pack on the basis of a 2.5:1 relativity. The PBAC agreed that the approach taken to re-calculating the price of the ezetimibe+rosuvastatin combination, but did not accept the relativity claimed (see Recommendation and Reasons).

The PBAC noted that, at the reduced price proposed in the pre-PBAC Response, the ezetimibe+rosuvastatin co-pack is less expensive than the ezetimibe/simvastatin FDC, and less expensive than ezetimibe and rosuvastatin administered concomitantly. This would result in a net saving to Government when ezetimibe+rosuvastatin co-pack replaces the ezetimibe/simvastatin FDC, or when it replaces the components administered concomitantly.

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 estimated the number of scripts over the first five years of listing to be more than $3 million.

The PBAC noted that revised financial estimates, based on the reduced proposed price, were presented in the pre-PBAC response. The revised figures estimated a saving of between $30 – 60 million to the PBS over the first 5 years of listing. The Committee noted that the revision of financial estimates also removed the assumptions about future price disclosure reductions, which the ESC advice had noted were inappropriately included in the submission's estimates.

The PBAC noted that the financial estimates would require further revision to reflect the price at which the Committee considers the cost-effectiveness of the new listing would be acceptable.

12. Recommendation and Reasons

The PBAC recommended Authority required (Streamlined) listing of ezetimibe + rosuvastatin 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. The PBAC considered that the cost-effectiveness of the combination drug ezetimibe+ rosuvastatin would be acceptable if it were cost-minimised against the combination drug atorvastatin+ezetimibe, with a relativity of rosuvastatin:atorvastatin of 1:2.2.

As was the case in their considerations of the ezetimibe + atorvastatin co-pack, the PBAC were of the view that there was no compelling clinical need for co-pack products, and remained concerned that it might inappropriately direct use away from adequate titration of statins given alone.

The PBAC agreed that the components (co administered) and the ezetimibe/simvastatin FDC were both relevant comparators. The Committee also considered that the ezetimibe+atorvastatin co-pack (recommended at the July 2013 PBAC meeting) was a relevant comparator.

The PBAC accepted the claim that the ezetimibe+rosuvastatin 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), and noted that no claim was made in the submission against the ezetimibe + atorvastatin co-pack.

The PBAC noted that the pre-PBAC Response offered a reduced price, such that the price of the ezetimibe + rosuvastatin co-pack was no higher than the price of the ezetimibe + atorvastatin co-pack, at a relativity of 1:2.5 for the statin component. Although not accepting the relativity proposed by the sponsor, the PBAC considered this approach was appropriate, as if treatment with the combination ezetimibe + rosuvastatin was substantially more costly than an alternative therapy or alternative therapies, the PBAC could only recommend listing of the combination if it is satisfied that the combination 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 combination atorvastatin + ezetimibe.

The Committee noted that the sponsor's proposed relativity of rosuvastin:atorvastatin of 1:2.5 reflected the relative ex-manufacturer prices of the two statins at the time rosuvastatin was listed. However this does not take account of the reference price driven price reductions (WAMTC) which have been applied to rosuvastatin since listing. When those are taken into account a relativity of 1:2.2 is appropriate (based on the approved ex-manufacture prices of the two drugs 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 further noted that in the 12 months to 30 June 2012,

Government expenditure on ezetimibe and the combination, ezetimibe + simvastatin, under the PBS was $60.5 million and $78.3 million respectively. The PBAC formed the 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.

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

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

In accordance with subsection 101(3BA) of the National Health Act 1953, the PBAC advised the Minister that it is of the opinion that, on the basis of the material available to it at its November 2013 meeting, ezetimibe + rosuvastatin co-pack should be treated as interchangeable on an individual patient basis with the ezetimibe + atorvastatin co-pack, and with the ezetimibe and simvastatin FDC.

Outcome:
Recommended

Add the following new items:

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

Condition:	Hypercholesterolaemia
Restriction:	Authority required (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	№.of Rpts	Proprietary Name and Manufacturer
EZETIMIBE AND ROSUVASTATIN			
Pack containing 30 tablets ezetimibe 10 mg and 30 tablets rosuvastatin 5 mg	1	5	Rosuzet MK

Condition:	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 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 considers that interchangeability between ROSUZET and VYTORIN is inconsistent with previous PBAC decisions and not warranted given that simvastatin and rosuvastatin were in separate therapeutic groups.