PUBLIC SUMMARY DOCUMENT
Product: Ezetimibe with simvastatin, tablet, 10 mg-20 mg, Vytorin®
Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd
Date of PBAC Consideration: March 2012

1. Purpose of Application

The submission requested an extension to the current Authority Required (Streamlined) listing to include the primary prevention of major cardiovascular events in a patient with moderate to severe chronic kidney disease, who does not fall into a category for which the General Statement for Lipid Lowering Drugs (GSLLD) allows PBS subsidised treatment with a statin.

2. Background

This drug had not previously been considered by the PBAC for the requested indication.

Ezetimibe with simvastatin is currently listed on the PBS as an Authority Required (STREAMLINED) benefit for the following indications:

- 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) (all strengths);
- Patients eligible for PBS-subsidised lipid-lowering medication (according to the criteria set out in the General Statement for Lipid-Lowering Drugs) where treatment with an HMG CoA reductase inhibitor (statin) must be reduced because the patient developed a clinically important product-related adverse event during treatment with a statin. (10 mg – 10 mg and 10 mg - 20 mg strengths only);
- Treatment, in conjunction with dietary therapy and exercise, in patients whose cholesterol levels are inadequately controlled with an HMG CoA reductase inhibitor (statin) and who have:
    - Coronary heart disease; or
    - Diabetes mellitus; or
    - Peripheral vascular disease; or
    - Heterozygous familial hypercholesterolaemia; or
    - Cerebrovascular disease which has become symptomatic; or
    - Family history of coronary heart disease; or
    - Hypertension. (10 mg-40 mg and 10 mg-80 mg strengths only)

3. Registration Status

As of 25 July 2013, ezetimibe with simvastatin 10 mg-20 mg is TGA registered for the following indications:

Primary Hypercholesterolaemia: as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate:

- Patients not appropriately controlled with a statin or ezetimibe alone.
- Patients already treated with a statin and ezetimibe.

Homozygous Familial Hypercholesterolaemia (HoFH): in patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).

The Clinical Trials section of the TGA approved Product Information includes information from the SHARP study in reference to the prevention of major vascular events in chronic kidney disease.

4. Listing Requested and PBAC's View

Authority Required (STREAMLINED)

Treatment, in conjunction with diet and exercise for the primary prevention of major cardiovascular events in patients with moderate to severe chronic kidney disease AND who do not fall into a category for which the GENERAL STATEMENT FOR LIPID LOWERING allows PBS subsidised treatment with a statin.

Moderate to severe chronic kidney disease is defined as persistent proteinuria or estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2, measured on at least two occasions over a three month period.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Patients with renal disease have an increased risk of cardiovascular disease.

The submission proposed that the place in therapy of ezetimibe with simvastatin in chronic kidney disease is for the primary prevention of major cardiovascular disease including death, stroke, myocardial infarction (MI) and revascularisation procedures, irrespective of the patient's lipid levels or the presence of existing cardiovascular disease.

For PBAC's view, see Recommendation and Reasons.

6. Comparator

The submission nominated placebo as the main comparator.

The PBAC considered that the appropriate comparator is treatment with a statin, and noted that the specific statin a clinician would choose to prescribe would not necessarily be simvastatin.

7. Clinical Trials

The submission presented one randomised trial (SHARP) comparing ezetimibe/simvastatin with placebo in 9,438 patients with chronic kidney disease (CKD).

Details of the published trial are shown below.

Trial ID / First author	Protocol title / Publication title	Publication citation
Direct randomised trial		
SHARP Baigent C, et al	The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with Chronic Kidney Disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial.	*Lancet.* 2011 Jun 25;377(9784):2181-9

For PBAC's view, see Recommendation and Reasons.

8. Results of Trials

The main results from the direct randomised trial (SHARP) for Major Vascular Events (MVE) and Major Atherosclerotic Events (MAE) are summarised in the table below.

Results of MVE and MAE (separate components) across the direct randomised trial (all patients, including those re-randomised from simvastatin)

Trial ID	Ezetimibe/ simvastatin n with event/N (%)	Placebo n with event/N (%)	RD (95% CI)	RR (95% CI)
MVE (MVE population)	**639/4193 (15.2%)**	**749/4191 (17.9%)**	**-2.6% (-4.2%, -1.0%)**	**0.84 (0.75-0.93) P=0.0010**
MVE (all patients)	**701/4650 (15.1%)**	**814/4620 (17.6%)**	**-2.5% (-4.0%, -1.0%)**	**0.85 (0.77-0.94) P=0.0012**
Major cardiac event	367/4650 (7.9%)	403/4620 (8.7%)	-0.8% (-2.0%, 0.3%)	0.90 (0.78-1.04) P=0.16
Any stroke	171/4650 (3.7%)	210/4620 (4.5%)	-0.9% (-1.7%, -0.1%)	0.81 (0.66-0.99) P=0.04
Any revasc. procedure	284/4650 (6.1%)	352/4620 (7.6%)	-1.5% (-2.5%, -0.5%)	0.79 (0.68-0.93) P=0.0036
Total MVE	701/4650 (15.1%)	814/4620 (17.6%)	-2.5% (-4.0%, -1.0%)	0.85 (0.77-0.94) P=0.0012
Heterogeneity (Chi_2^2) = 1.7 (P=0.44)				
MAE (all patients)	**526/4650 (11.3%)**	**619/4620 (13.4%)**	**-2.1% (-3.4%, -0.7%)**	**0.83 (0.74-0.94) P=0.0022**
Major coronary event	213/4650 (4.6%)	230/4620 (5.0%)	-0.4% (-1.3%, 0.5%)	0.92 (0.76-1.11) P=0.37
Ischemic stroke	131/4650 (2.8%)	174/4620 (3.8%)	-0.9% (-1.7%, -0.2%)	0.75 (0.60-0.94) P=0.01
Any revasc. procedure	284/4650 (6.1%)	352/4620 (7.6%)	-1.5% (-2.5%, -0.5%)	0.79 (0.68-0.93) P=0.0036
Total MAE	526/4650 (11.3%)	619/4620 (13.4%)	-2.1% (-3.4%, -0.7%)	0.83 (0.74-0.94) P=0.0022
Heterogeneity (Chi_2^2) = 2.2 (P=0.33)				
Progression to End-Stage Renal Disease (ESRD) by pre-dialysis patients	**1057/3117 (33.9%)**	**1084/3130 (34.6%)**	**-0.7% (-2.5%, 1.1%)**	**0.97 (0.89-1.05) P=0.41**

The PBAC noted that results from the SHARP trial showed that ezetimibe/simvastatin significantly decreased the risk of both MVE and MAE in patients with CKD. This was driven by decreases in the risk of strokes and revascularisation procedures. Cardiac deaths, coronary deaths or non-fatal myocardial infarctions (MIs) were not significantly decreased, and coronary deaths were slightly higher for patients treated with ezetimibe/simvastatin, however it was noted that the study was not powered to detect a difference in these sub-components.

For PBAC's view, see Recommendation and Reasons.

The table below summarises the main adverse events from the direct randomised trial (SHARP) during the entire follow-up period in 9,270 patients.

Principal Safety Data Categories

	Ezetimibe/simvastatin (N=4650) n (%)	Placebo (N=4620) n (%)	P-value
Deaths	1142 (24.6%)	1115 (24.1%)	*0.63*
Development of diabetes	172 (4.8%)	162 (4.5%)	*0.59*
Cancers	438 (9.4%)	439 (9.5%)	*0.89*
Non-Endpoint# SAEs	3258 (70.1%)	3270 (70.8%)	*0.43*
SAEs Considered Drug-Related	20 (0.43%)	13 (0.28%)	NR
SAEs Considered Drug-Related Causing discontinuations**	17 (0.4%)	12 (0.3%)	NR
Other SAEs Causing Discontinuation	297 (6.4%)	307 (6.6%)	NR
Myopathy/Rhabdomyolysis	8 (0.17%)	3 (0.065%)	NR
Non-Infective Hepatitis	5 (0.11%) *Should be 6 (0.13%)*	4 (0.09%)	NR
Persistently increased transaminases (>3xULN on 2 consecutive measurements)	30 (0.65%)	26 (0.56%)	NR

SAE = serious adverse events, ULN=upper limit of normal, CK = creatine kinase. # Excludes deaths, major vascular events, cancer, TIA, hospitalization for angina or heart failure, dialysis access revision, diabetes and hypoglycaemia, initiation of dialysis, pancreatitis, hepatitis, myopathy and rhabdomyolysis. **4 patients (3 ezetimibe/simvastatin and 1 placebo) had a suspected serious adverse reaction but continued taking study medication.

The overall incidence of serious adverse events (SAEs) and adverse events leading to discontinuation of study medication was similar in the two groups. There was no significant difference in all non-fatal SAEs (p=0.43). There was no significant imbalance in any particular SAE in patients randomized to ezetimibe/simvastatin, with the exception of haemodialysis access (excluding revision) which was less frequent in patients allocated to ezetimibe/simvastatin. More SAEs considered to be drug related were observed in patients taking ezetimibe/simvastatin, and more suspected serious adverse reactions leading to discontinuation of ezetimibe/simvastatin; however the p-values were not reported. The most common suspected serious adverse reaction that led to discontinuation of ezetimibe/simvastatin was renal transplantation (often because of starting cyclosporine).

9. Clinical Claim

The submission described ezetimibe/simvastatin as superior in terms of comparative effectiveness and similar in terms of comparative safety over placebo. However, the PBAC noted that the incidence of myopathy and rhabdomyolysis was increased with ezetimibe/simvastatin compared to placebo and considered that the claim of similar safety may not be appropriate.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a stepped and modelled economic evaluation. A Markov model with 24 health states was used to synthesise costs and effectiveness data from a variety of sources. The health states reflected combinations of cardiovascular (CV) events (no event, post revascularisation, post MI, post stroke), CKD health states (pre-dialysis, on dialysis and post-transplant), treatment status (ezetimibe/simvastatin or placebo), and two death states (CV death and non-CV death). The post-transplant state was only included in the sensitivity analysis. The health states were hierarchical and patients could not transition to a better health state. The cycle length was 3 months and a lifetime horizon

was assumed. In the model patients on treatment were at risk of discontinuing treatment, in which case the risk of CV events in both arms was equal to that experienced with placebo. Patients not on treatment would initiate treatment (statin therapy in placebo arm) if they experienced a CV event, in which case the risk of CV events in both arms was equal to that experienced with ezetimibe/simvastatin. The PBAC agreed with the ESC that in clinical practice, patients in the comparator arm were likely to become eligible for statin therapy under the GSLLD criteria earlier than their first CV event. The direction of impact of this on the incremental cost-effectiveness ratio (ICER) was uncertain as costs and efficacy would both increase in the placebo arm.

The outcomes used in the modelled economic evaluation were: cardiovascular death, non-fatal stroke (ischaemic and unknown stroke), non-fatal MI, and revascularisation procedure. These outcomes were transformed to life years and quality adjusted life years (QALYs) gained. The model used individual events from the trial, and these events were re-distributed such that they were mutually exclusive. Differential risks of events were used in the economic model despite there being lack of a significant effect against CV death and non-fatal MIs. Furthermore, by adding stroke deaths to CV deaths the relative risk improved in favour of ezetimibe/simvastatin. The model used a lower risk of progression to end stage renal disease (ESRD) with ezetimibe/simvastatin, despite the trial finding no statistically significant difference.

The base case incremental cost per extra QALY gained was between $45,000 and $75,000.

The PBAC noted that the model results and key sensitivity analyses were particularly sensitive to assumptions regarding the risk of progression to ESRD and risk of cardio vascular disease (CVD) death.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients treated per year to be in the range of 10,000 – 50,000 in Year 5 of listing at a net cost to the PBS of between $10 – 30 million in Year 5 of listing.

The PBAC considered there was potential for the net cost to the PBS to be greater than the estimate in the submission, due to an underestimation of total scripts in the submission.

12. Recommendation and Reasons

The PBAC noted that this submission is being considered under the Therapeutic Goods Administration (TGA)/PBAC parallel process and that neither the TGA Clinical Evaluator's Report nor the Delegate's Summary had been received. The PBAC further noted that the US Food and Drug Administration's Endocrinologic and Metabolic Drugs Advisory Committee recommended ezetimibe/simvastatin for use in pre-dialysis CKD patients, but not for patients with end-stage renal disease receiving dialysis.

The PBAC noted that if ezetimibe/simvastatin was approved for this extension to existing restrictions it would identify the only population eligible for first line treatment with the

combination of ezetimibe/simvastatin in a situation where statin alone is currently not PBS subsidised. However, the PBAC noted that approximately 35-41% of CKD patients not satisfying the General Statement for Lipid Lowering Drugs (GSLLD) prescribed as Pharmaceutical Benefits criteria are currently receiving statin therapy.

The PBAC noted that the applicability of the data to the requested PBS population was limited by a number of differences. In particular inconsistencies in the definition of moderate to severe CKD between the submission (eGFR less than 60 ml/min/1.73 m^2) and the unpublished draft Guidelines for the Management of Absolute Cardiovascular Diseases Risk 2011 (eGFR less than 45 ml/min/1.73 m^2). The PBAC considered that the definition of moderate to severe CKD should be consistent with the clinical management algorithm from the Guidelines. The Committee also noted that the clinical management algorithm presented in the submission accounted for patients with CKD who are not initially eligible for statin therapy under the GSLLD criteria, but not those patients who later become eligible for statin therapy. The algorithm also assumed no difference in the treatment of patients requiring dialysis and did not adequately assess the option of using simvastatin, or any other statin, alone or before ezetimibe/simvastatin.

The basis of the submission was one randomised trial (SHARP) comparing ezetimibe/simvastatin with placebo in patients with CKD. However, the PBAC considered that the Cochrane review and other trials identified during the evaluation would have been useful to inform a comparison of simvastatin, or another statin, to placebo. The PBAC noted that the SHARP trial did not include any patients on statins alone although many (approximately 50%) would have qualified for statins under PBS, therefore the incremental benefit of adding ezetimibe to statin therapy is not addressed in the submission and therefore remains unknown.

The results from the SHARP trial showed that ezetimibe/simvastatin significantly decreased the risk of both Major Vascular Events (MVE) and Major Atherosclerotic Events (MAE) in patients with CKD. This was driven by decreases in the risk of strokes and revascularisation procedures. There was no significant decrease in the risk of progression to End-Stage Renal Disease (ESRD) in pre-dialysis patients (32% of trial patients had ESRD at baseline). However, the PBAC noted that the estimated reduction in MVE and MAE in pre-dialysis patients (22%) in SHARP was similar to the estimated reduction in CV deaths (20%) and non-fatal CV-events (25%) reported in the published Cochrane review on statin therapy for pre-dialysis patients with CKD. The PBAC considered the possibility that the benefit observed in SHARP could be achieved with statin therapy alone, and that the addition of ezetimibe does not increase the benefit, could not be excluded based on the data provided.

The PBAC considered that the treatment effect used in the model, based on the entire ITT population, was not appropriate as it included part of the trial population who would already be eligible for statin therapy, and therefore does not reflect the additional patient population that would gain access to ezetimibe/simvastatin under the proposed listing. The PBAC noted that the model results and key sensitivity analyses are particularly sensitive to assumptions regarding the risk of progression to ESRD and risk of CVD death. The PBAC considered there was uncertainty around the assumptions and estimates used in the model and that the ICERs were high and unacceptable.

The PBAC rejected the submission on the basis of an inappropriate clinical management algorithm and high and unacceptable cost-effectiveness, noting also that TGA had not yet approved the indication. The PBAC considered that "Option 2" of the Pre-PBAC response might be more appropriate. This proposed a general change to the GSLLD to add CKD as another high risk category, and would thus enable ezetimibe/simvastatin to be used as second line.

The PBAC noted that the submission meets the criteria for an Independent Review.

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 looks forward to working with the PBAC to make ezetimibe/ simvastatin 10/20 available for CKD patients that are currently not eligible to receive statin treatment.