PUBLIC SUMMARY DOCUMENT

Product: EZETIMIBE, tablet, 10 mg, Ezetrol®; EZETIMIBE with SIMVASTATIN, tablets, 10 mg-40 mg, 10 mg-80 mg, Vytorin®

Sponsors: Merck Sharp & Dohme (Australia) Pty Ltd Schering Plough Pty Ltd

Date of PBAC Consideration: November 2005

1. Purpose of Application

To add three conditions (symptomatic peripheral vascular disease; symptomatic cerebrovascular disease; and heterozygous familial hypercholesterolaemia) to the ezetimibe listing for co-administration with a statin in patients eligible for subsidised lipid lowering medication with coronary heart disease or diabetes mellitus, whose cholesterol levels are inadequately controlled with a statin.

2. Background

At the June 2003 meeting, the PBAC recommended an authority required listing for ezetimibe for:

(1) patients who were eligible to receive lipid lowering medication when statins were unsuitable or contraindicated;

(2) homozygous sitosterolemia; and

(3) patients with homozygous familial hypercholesterolemia in combination with a statin.

At its December 2003 meeting, the PBAC recommended listing in patients eligible for subsidised lipid lowering medication, with coronary heart disease and/or diabetes mellitus, on the basis of acceptable cost-effectiveness. Also at this meeting, listing for heterozygous familial hypercholesterolemia (HeFH) was rejected because of uncertain clinical benefit and the resulting uncertain cost-effectiveness.

Ezetrol was listed 1 August 2004.

The March 2005 PBAC meeting recommended listing of ezetimibe with simvastatin on a cost-minimisation basis compared to the sum of the corresponding strengths of the individual components.

The July 2005 PBAC meeting amended the previously recommended restriction for ezetimibe with simvastatin to allow for patients with coronary heart disease or diabetes mellitus who were inadequately controlled after three months treatment at a daily dose of 40 mg or greater of any statin to commence treatment.

Vytorin was listed on 1 February 2006.

3. Registration Status

Ezetimibe (Ezetrol)

Primary Hypercholesterolaemia: Ezetrol administered alone, or with an HMG-CoA reductase inhibitor (statin), is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia.

Homozygous Familial Hypercholesterolaemia (HoFH): Ezetrol, administered with a statin, is indicated for patients with HoFH. Patients may also receive adjuctive treatments (e.g. LDL apheresis).

Homozygous Sitosterolaemia (Phytosterolaemia): Ezetrol is indicated for the reduction of elevated sitosterol and campestrol levels in patients with homozygous familial sitosterolaemia.

Ezetimibe with Simvastatin (Vytorin)
Vytorin is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolemia or mixed hyperlipidemia where use of combination product is appropriate: Patients not appropriately controlled with a statin or ezetimibe alone. Patients already treated with a statin and ezetimibe. Vytorin is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).

4. Listing Requested and PBAC's View

EZETIMIBE
Authority required
Initial treatment for co-administration with an HMG CoA reductase inhibitor (statin) in patients whose cholesterol levels are inadequately controlled with a statin and who have:
(a) coronary heart disease; or
(b) diabetes mellitus; or
(c) symptomatic peripheral vascular disease; or
(d) symptomatic cerebrovascular disease; or
(e) heterozygous familial hypercholesterolaemia.
Inadequate control with a statin is defined as a cholesterol level in excess of the initial threshold for PBS-subsidy according to the General Statement for Lipid-Lowering Drugs after at least 3 months of treatment at a daily dose of 40 mg or greater of a statin.
The cholesterol level after 3 months of treatment with a statin and the dose of the statin must be provided at the time of application. The cholesterol level results provided must be no more than 1 month old at the time of application;

Continuing treatment for co-administration with HMG CoA reductase inhibitors (statins) in patients with coronary heart disease or diabetes mellitus or symptomatic peripheral vascular disease or symptomatic cerebrovascular disease or heterozygous familial hypercholesterolaemia whose cholesterol levels were inadequately controlled with a statin, where the patient has previously been issued with an authority prescription for this drug.

EZETIMIBE with SIMVASTATIN
Authority required
Initial treatment in patients whose cholesterol levels are inadequately controlled with a HMG CoA reductase inhibitor (statin) and who have:
(a) coronary heart disease; or
(b) diabetes mellitus; or
(c) symptomatic peripheral vascular disease; or
(e) symptomatic cerebrovascular disease; or
(f) heterozygous familial hypercholesterolaemia.

Inadequate control with a statin is defined as a cholesterol level in excess of the initial threshold for PBS-subsidy according to the General Statement for Lipid Lowering Drugs after at least 3 months of treatment at the daily dose of 40 mg or greater of a statin.

The cholesterol level after 3 months of treatment with a statin and the dose of the statin must be provided at the time of application. The cholesterol levels provided must be no more than 1 month old at the time of application.

Continuing treatment in patients with coronary heart disease or diabetes mellitus or symptomatic peripheral vascular disease or symptomatic cerebrovascular disease or heterozygous familial hypercholesterolaemia whose cholesterol levels were inadequately controlled with a statin, where the patient has previously been issued with an authority prescription for this item or the combination of ezetemibe and 40 mg or greater of a statin.

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).

The PBAC noted that lipid levels for treatment of cerebrovascular disease are not included in the current General Statement for Lipid-Lowering Drugs. For more on the PBAC's view, *see Recommendation and Reasons.*

5. Clinical Place for the Proposed Therapy

A portion of high risk patients are not achieving sufficient lowering of cholesterol on statin therapy alone, even at maximal recommended or tolerated doses. In such patients the addition of ezetimibe, which has a complementary mechanism of action, provides incremental lipid lowering and facilitates the attainment of treatment goals.

6. Comparator

The PBAC accepted the submission's nomination of placebo co-administered with a statin (dose not qualified) as the appropriate main comparator.

7. Clinical Trials

The submission included the two key trials that were previously considered at the June and December 2003 PBAC meetings (i.e. the P00693 Atorvastatin Filter Study and P02173/P02246 Ezetimibe Add-on Study). Seven supportive trials comparing ezetimibe co-administered with statins with statins alone in adults with cardiovascular heart disease (CHD) and/or diabetes and/or CHD-risk equivalents over 6 to 24 weeks were also presented. Below are details relating to the key trials.

Trial/First author	**Protocol title**	**Publication citation**
P00693 Stein E	Atorvastatin Filter Study	*Am Heart J* 2004; 148(3):447-55.
P02173; P02246/ 1) Gagne C 2) Simons L	Ezetimibe Add-on Study	1) *Am J Cardiol* 2002; 90:1084-91. 2) *Curr Med Res Opin* 2004; 20(9):1437-45

8. Results of Trials

The results of the key trials are summarised in the tables below.

Proportion of patients achieving LDL-C target at trial endpoint

P02173/P02246 Ezetimibe Add-On Study	Ezetimibe with statin	Statin alone	Difference (95% CI)
NCEP ATP II target levels*	218/309 (71.5%)	61/323 (18.9%)	**52% (45, 58)**#
P00693 Atorvastatin Filter Study	Ezetimibe with	Atorvastatin up-	Difference (95% CI)

	atorvastatin up-titration	titration alone	
LDL-C ≤2.59mmol/L	67/305 (22%)	23/316 (7%)	**15% (9, 20)**##

NCEP ATP II = National Cholesterol Education Program Adult Treatment Panel.
LDL-C = Low-density lipoprotein cholesterol.
*Patients above target levels at baseline
#p<0.001 ##p<0.01

Mean percent change of lipid parameters from baseline to trial endpoint *(unless otherwise indicated)*

P02173/P02246 Ezetimibe Add-on Study	Ezetimibe with statin (N=379)	Statin alone (N=390)	Difference (95% CI) (p<0.001)
LDL-C Total-C HDL-C TG	-25.14% -17.06% 2.66% -13.95%	-3.67% -2.31% 0.99% -2.87%	**-21.5% (-23.5, -19.5)** **-14.7% (-16.2, -13.3)** **1.7% (0.3, 3.1)#** NR
SUB-GROUP CHD, and/or diabetes mellitus and LDL-C ≥2.59mmol/L Mean (SD) percent change for LDL-C	N=243 *-25.0% (15.6)*	N=274 *-3.6% (13.6)*	***-21.4 (-23.9, -18.9)***
P00693 Atorvastatin Filter Study	Ezetimibe with atorvastatin up-titration (N=305)	Atorvastatin up-titration alone (N=316)	Difference (95% CI) (p<0.01)
LDL-C (at Week 4)* Total-C (at Week 4)* Total-C (at endpoint) HDL-C (at Week 4)* HDL-C (at endpoint) TG (at Week 4)	-22.7% -17.34% -24.37% 2.13% 3.60% -6.10%	-8.55% -6.08% -14.89% 1.25% 1.00% -1.78%	**-14.22% (-16.24, -12.20)** **-11.26% (-12.79, -9.73)** NR 0.88% (-0.71, 2.46) NR **-7.88% (-12.08, -3.68)**

* At Week 4, maximum titration of atorvastatin had not occurred in the 14-week treatment period
Total-C = Total cholesterol, HDL = High-density lipoprotein cholesterol, TG = Triglycerides,
LDL-C = Low-density lipoprotein cholesterol.
#p<0.05

Generally, the outcomes reported in the trials were the mean percent change from baseline of lipid parameters and the proportion of patients achieving target LDL-C levels. These outcomes were variously defined as either primary or secondary outcomes in the trials.

There were significantly more patients who achieved target LDL-C levels (variously defined depending on trial, favouring ezetimibe co-administered with statins compared to statins alone. Overall, differences in mean LDL-C percent change from baseline to endpoint across the trials also significantly favoured the ezetimibe co-administered with statin treatment groups.

Results for the sub-groups also significantly favoured the ezetimibe co-administered with statins group. No results were reported for the sub-group of patients with symptomatic CVD and symptomatic PVD, although some of these patients may be present in the sub-group of patients with CHD risk equivalents.

Results from Protocol P00693 Atorvastatin Filter Study: HeFH sub-group

	Ezetimibe 10mg co-administered with up-titration of atorvastatin (N=181)	**Up-titration of atorvastatin alone (N=181)**
Proportion achieving LDL-C ≤2.59mmol/L **at Week 14**	31/181 (17%)	8/181 (4%)
Difference (95% CI)	**13% (6%, 19%)**	
LDL-C (direct)		

Mean percent change **at Week 4** [*] from baseline (%) Difference (95% CI)	-23.59 **-16.15 (-18.78, -13.52)#**	-7.44
Total-C Mean percent change **at Week 4** [*] from baseline (%) Difference (95% CI)	-18.10 **-12.60 (-14.64, -10.57)#**	-5.50
Triglycerides Mean percent change **at Week 4** [*] from baseline (%) Difference (95% CI)	-5.82 **-8.82 (-14.39, -3.25)#**	3.00
HDL-C Mean percent change **at Week 4** [*] from baseline (%) Difference (95% CI)	1.90 1.16 (-0.92, 3.24)	0.75

Bolded numbers indicate statistically significant difference, p<0.01
[*] At Week 4, maximum titration of atorvastatin had not occurred in the 14-week treatment period

The above table shows that in the heterozygous HeFH sub-group, a statistically significant difference for ezetimibe co-administered with atorvastatin compared to atorvastatin alone was reported for LDL-C, Total-C and TG at four weeks.

The PBAC noted that, generally, there were no differences in the percentage of subjects reporting adverse effects between any randomised groups.

9. Clinical Claim

The PBAC accepted that ezetimibe co-administered with statins is associated with significant advantages in effectiveness over statins alone.

10. Economic Analysis

A preliminary economic evaluation was presented. The PBAC considered that the adoption of a cost-effectiveness approach was appropriate. The resources included were the costs of ezetimibe and statins only.

The modelled economic evaluation presented also adopted a cost-effectiveness approach, using a Markov state transition model to obtain cost per life-years gained. The PBAC also considered this approach appropriate. The average duration of the model was about 30 years. The resources included were drug costs, costs of cardiovascular heart disease death, cost of myocardial infarction and cost of angina.

The incremental cost/extra life year gained in cerebrovascular disease patients, peripheral vascular disease patients and HeFH patients was between $15,000-$45,000.

11. Estimated PBS Usage and Financial Implications

The submission estimated use by up to 10,000-50,000 patients with symptomatic cerebrovascular disease and/or symptomatic peripheral vascular disease and up to 2,000-10,000 patients with HeFH in Year 4 of listing.

The financial cost was estimated to be up to $5-10 million in Year 5 of listing.

12. Recommendation and Reasons

The PBAC recommended the addition of two indications to the current listing for ezetimibe, namely peripheral vascular disease and heterozygous familial hypercholesterolaemia, on the basis of acceptable cost-effectiveness in these patient groups. The PBAC was unable to agree

to the addition of cerebrovascular disease because the current General Statement for Lipid-Lowering Drugs does not include this patient group.

Recommendation

EZETIMIBE, tablet, 10 mg

Amend restriction for use in patients who have coronary heart disease or diabetes mellitus to read:

Restriction:	Authority required Initial treatment, in conjunction with dietary therapy and exercise, for co-administration with an HMG CoA reductase inhibitor (statin) in patients whose cholesterol levels are inadequately controlled with a statin and who have: (a) coronary heart disease; or (b) diabetes mellitus; or (c) peripheral vascular disease; or (d) heterozygous familial hypercholesterolaemia. Inadequate control with a statin is defined as a cholesterol level in excess of the initial threshold for PBS-subsidy according to the General Statement for Lipid-Lowering Drugs after at least 3 months of treatment at a daily dose of 40 mg or greater of a statin in conjunction with dietary therapy and exercise. The cholesterol level after 3 months of treatment with a statin and the dose of the statin must be provided at the time of application. The cholesterol level results provided must be no more than 1 month old at the time of application; Continuing treatment for co-administration with HMG CoA reductase inhibitors (statins) in patients with coronary heart disease or diabetes mellitus or peripheral vascular disease or heterozygous familial hypercholesterolaemia whose cholesterol levels were inadequately controlled with a statin, where the patient has previously been issued with an authority prescription for this drug.
Maximum quantity	30
Repeats:	5

Recommendation and Reasons

The PBAC recommended the addition of two indications to the current recommended listing for ezetimibe with simvastatin, namely peripheral vascular disease and heterozygous familial hypercholesterolaemia, on the basis of acceptable cost-effectiveness in these patient groups. The PBAC was unable to agree to the addition of cerebrovascular disease because the current General Statement for Lipid-Lowering Drugs does not include this patient group.

Recommendation

EZETIMIBE with SIMVASTATIN, tablets, 10 mg-40 mg, 10 mg-80 mg

Amend recommended restriction to read:

Restriction:	Authority required Initial treatment, in conjunction with dietary therapy and exercise, in patients whose cholesterol levels are inadequately controlled with a HMG CoA reductase inhibitor (statin) and who have:

(a) coronary heart disease; or
(b) diabetes mellitus; or
(c) peripheral vascular disease; or
(d) heterozygous familial hypercholesterolaemia.

Inadequate control with a statin is defined as a cholesterol level in excess of the initial threshold for PBS-subsidy according to the General Statement for Lipid Lowering Drugs after at least 3 months of treatment at the daily dose of 40 mg or greater of a statin, in conjunction with dietary therapy and exercise.
The cholesterol level after 3 months of treatment with a statin and the dose of the statin must be provided at the time of application. The cholesterol level results provided must be no more than 1 month old at the time of application;

Continuing treatment in patients with coronary heart disease or diabetes mellitus or peripheral vascular disease or heterozygous familial hypercholesterolaemia where the patient has previously been issued with an authority prescription for this item or the combination of ezetimibe and 40 mg or greater of a statin.

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).

Maximum quantity 30
Repeats: 5

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