PUBLIC SUMMARY DOCUMENT

Product: Ezetimibe, tablet, 10 mg, Ezetrol®, and Ezetimibe with Simvastatin, tablet, 10 mg – 10 mg, 10 mg – 40 mg and 10 mg – 80 mg, Vytorin®

Sponsor: Merck Sharp and Dohme (Australia) Pty Ltd

Date of PBAC Consideration: November 2006

1. Purpose of Application

1) The submission requested an extension to the current authority required PBS listing of ezetimibe and ezetimibe with simvastatin to include the treatment of patients with hypertension, a family history of coronary heart disease (Part A) or high dose statin intolerance (Part B).

2) The submission requested a new strength of ezetimibe with simvastatin (10 mg – 10 mg) to be listed.

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 hypercholesterolaemia in combination with a statin.

The PBAC rejected use when co-administered with statins in patients eligible for subsidised lipid lowering medication, with coronary heart disease and/or diabetes mellitus, because of uncertain cost-effectiveness.

At its December 2003 meeting the PBAC recommended listing for patients with coronary heart disease or diabetes mellitus on the basis of acceptable cost-effectiveness, noting that although there were residual uncertainties over the modelling, these were insufficient to cast doubt on the overall acceptability of the conclusions. Also at this meeting, listing for heterozygous familial hypercholesterolaemia (HeFH) was rejected because of uncertain clinical benefit and the resulting uncertain cost-effectiveness.

Ezetrol was first listed on 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 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 40 mg or greater of any statin to commence treatment on Vytorin® (ezetimibe with simvastatin), rather than require patients treated with other statins to take 3 months of concomitant treatment with ezetimibe and simvastatin prior to commencing the combination product.

At the November 2005 meeting, the PBAC recommended the addition of two indications to the current listing for ezetimibe and ezetimibe and simvastatin, namely peripheral vascular disease and heterozygous familial hypercholesterolaemia, on the basis of acceptable cost-effectiveness in these patient groups. These changes were effective 1 April 2006. The PBAC was unable to agree to the addition of cerebrovascular disease because the General Statement for Lipid-Lowering Drugs current at the time did not include this patient group. However, the Committee indicated that it had no objection to the inclusion of this patient group if and when the recommended changes to the General Statement occurred.

Vytorin was first listed on 1 February 2006.

On 5 September 2006, an announcement was made that the new General Statement for Lipid Lowering Drugs as recommended by the PBAC will be implemented on 1 October 2006. The patient categories may be found at the following website:

http://www.health.gov.au/internet/wcms/publishing.nsf/content/lipid_eligibilitycriteria.htm

Changes to the lipid levels required for PBS access to EZETROL and VYTORIN and inclusion of access for patients with symptomatic cerebrovascular disease also took effect from 1 October 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 adjunctive treatments (e.g. LDL apheresis).

Homozygous Sitosterolaemia (Phytosterolaemia): Ezetrol is indicated for the reduction of elevated sitosterol and campesterol 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) hypercholesterolaemia 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 homozygous familial hypercholesterolaemia (HoFH). Patients may also receive adjunctive treatments (e.g., LDL apheresis).

4. Listing Requested and PBAC's View

(Part A - For the indication of family history of coronary heart disease or hypertension)

EZETROL

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; or
(e) family history of coronary heart disease; or
(f) hypertension

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 or family history of coronary heart disease or hypertension whose cholesterol levels were inadequately controlled with a statin, where the patient has previously been issued with an authority prescription for this drug.

EZETROL
(Part B - For the indication of intolerance of high dose statins)
Authority required
Initial treatment, in conjunction with dietary therapy and exercise, for co-administration with up to 10 mg of a HMG CoA reductase inhibitor (statin) in patients eligible for PBS subsidised lipid lowering medication (according to the criteria set out in the General Statement for Lipid Lowering Drugs) who are unable to tolerate 20 mg or greater of a statin due to a contraindication or experience of a clinically important adverse event (as defined in the ezetimibe monotherapy listing) and whose cholesterol levels are inadequately controlled with up to 10 mg of a statin.

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 up to 10 mg 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 up to 10 mg of a statin in patients whose cholesterol levels were inadequately controlled with up to 10 mg of a statin, where the patient has previously been issued with an authority prescription for this drug.

EZETIMIBE with SIMVASTATIN
(Part A - For the indication of family history of coronary heart disease or hypertension)
Authority required
Initial 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:

(a) coronary heart disease; or
(b) diabetes mellitus; or
(c) peripheral vascular disease; or
(d) heterozygous familial hypercholesterolaemia; or
(e) family history of coronary heart disease; or
(f) hypertension.

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 in patients with coronary heart disease or diabetes mellitus or peripheral vascular disease or heterozygous familial hypercholesterolaemia or family history of coronary heart disease or hypertension 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 ezetimibe and 40 mg or greater of a statin.

NEW STRENGTH – Vytorin 10/10
Authority required
Initial treatment, in conjunction with dietary therapy and exercise, with VYTORIN 10/10 in patients eligible for PBS subsidised lipid lowering medication (according to the criteria set out in the General Statement for Lipid Lowering Drugs) who are unable to tolerate 20 mg or greater of a statin due to a contraindication or experience of a clinically important adverse event (as defined in the ezetimibe monotherapy listing) and whose cholesterol levels are inadequately controlled with 10 mg of a statin.

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 10 mg 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 with VYTORIN 10/10 in patients whose cholesterol levels were inadequately controlled with 10 mg of a statin, where the patient has previously been issued with an authority prescription for this item or the combination of ezetimibe and 10 mg of a statin.

For PBAC's view, see Recommendations and Reasons.

5. Clinical Place for the Proposed Therapy

Part A - For the indication of family history of coronary heart disease or hypertension:
Family history of coronary heart disease and hypertension both appear to significantly elevate the risk of developing coronary heart disease (CHD) in both men and women.

Ezetimibe, a cholesterol absorption inhibitor, has a complementary action to the statins and provides incremental lipid lowering in patients where adequate lipid lowering has not been achieved with statins alone, even at maximal recommended doses or tolerated doses

Vytorin, a combination of ezetimibe with simvastatin, has similar effectiveness as the individual components simvastatin and ezetimibe, but with the added convenience of a single tablet.

Part B - For the indication of intolerance of high dose statins:
Some patients treated with statins are at increased risk of clinically important adverse events which require the interruption or discontinuation of therapy. Such events are more likely to occur at higher statin doses. Ezetimibe monotherapy may be an option for these patients. In other patients a low dose of statin treatment can be tolerated without apparent clinical symptoms. In these patients the benefits of lipid lowering with a low dose of statin may outweigh the risk of sub-clinical treatment side-effects.

Ezetimibe may be used as a treatment alternative for patients who are inadequately controlled on up to 10 mg of a statin and who are unable to tolerate a higher dose of statin demonstrated by a contraindication or experience of a clinically important event.

Vytorin 10 mg/10 mg (ezetimibe with simvastatin) may also be used for patients who are unable to tolerate 20 mg or more of a statin, and are inadequately controlled on 10 mg of a statin.

6. Comparator

For the indication of family history of coronary heart disease or hypertension (Part A):
The submission nominated placebo (co-administered with a statin). The PBAC advised that up-titration with a statin could be considered as an alternative comparator.

For the indication of intolerance of high dose statins (Part B):
The submission nominated placebo. The PBAC advised that ezetimibe monotherapy could also be a relevant comparator.

See Recommendations and Reasons.

7. Clinical Trials

For the indication of family history of coronary heart disease or hypertension (Part A):
The submission presented a meta-analysis of six trials where ezetimibe was compared with placebo as add-on therapy to a statin. In these 6 key studies patients primarily had established coronary heart disease (CHD) or were CHD risk equivalent. Several of the studies contained smaller populations of patients with 2 or more CHD risk factors. Sub-analysis by National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) categories showed little difference in the treatment effect between risk categories.

For the indication of intolerance of high dose statins (Part B):
The submission provided a meta-analysis of the same six trials presented in part A above. In the trials ezetimibe is compared with placebo as add-on therapy to a statin in patients who primarily have established CHD or who are CHD risk equivalent. The submission also included the results from a "before-and-after" study reported by Wierzbicki et al, 2005, conducted in patients with familial hypercholesterolaemia who had not achieved NCEP ATP III targets despite maximally tolerated doses of statins, and where ezetimibe was added as additional therapy to maximally tolerated dose of statins.

The submission provided 65 citations relating to the 19 included randomised controlled trials which supported the two concurrent requested listings. The key clinical papers for the published trials are listed below:

Trial	Description	Citations
Protocol 005	Randomised, double-blind placebo-controlled, multicentre trial of 12 weeks in patients with primary hypercholesterolaemia.	
Goldberg et al.		Mayo Clin Proc 2004; 79(5):620-629.
Protocol 021	Randomised, double-blind, parallel, multicentre trial of 30 weeks comprising of a 6-week, open-label simvastatin 20mg lipid stabilisation period and a 24-week treatment period in type 2 diabetic patients treated with thiazolidinediones.	
Gaudiani et al.		Diabetes, Obesity and Metabolism. 2005; 7(1): 88-97.
Protocol 023	Randomised, double-blind, parallel group, multicentre trial of 23 weeks in patients with CHD or CHD risk equivalent as defined by the NCEP Adult Treatment Panel III guidelines.	
Feldman et al.		Am J Cardiol 2004; 93(12):1481-1486.
Protocol 025	Randomised, double-blind, parallel group, multicentre trial of 28 weeks in patients with hypercholesterolaemia.	
Ballantyne et al.		Am J Cardiol 2004; 93(12):1487-1494.
Protocol 038	Randomised, double-blind, placebo-controlled, multicentre factorial trial of 12 weeks in patients with primary hypercholesterolaemia.	
Bays et al.		Clin Ther 2004; 26(11): 1758-1773.
Protocol 051	Randomised, double-blind, parallel group, multicentre trial of 6 weeks in patients with primary hypercholesterolaemia.	
Ballantyne et al.		Am Heart J 2005; 149(3): 464-73.
Protocol 058	Randomised, double-blind, parallel group, multicentre trial of 6 weeks in patients with primary hypercholesterolaemia.	
Abate et al.		J. Am. Geriatric Society 2006; 54(4, Suppl.):S163-S163 (#D22).
Protocol 679	Randomised, double-blind, placebo-controlled, multicentre trial of 12 weeks in patients with primary hypercholesterolaemia.	
Kerzner et al.		Am J Cardiol 2003; 91(4): 418-424, 2003.
Protocol 680	Randomised, double-blind, placebo-controlled, multicentre trial of 12 weeks in patients with primary hypercholesterolaemia.	
Davidson et al.		J Am Coll Cardiol 2002; 40(12): 2125-2134.

Trial	Description	Citations
Sager et al.		Am J Cardiol 2003; 92(12): 1414-1418.
Protocol 691	Randomised, double-blind, placebo-controlled, multicentre trial of 12 weeks in patients with primary hypercholesterolaemia.	
Melani et al.		Eur Heart J 2003; 24(8): 717-728.
Protocol 692	Randomised, double-blind, placebo-controlled, multicentre trial of 12 weeks in patients with primary hypercholesterolaemia.	
Ballantyne et al.		Circulation 2003; 107(19): 2409-2415.
Protocol 693	Randomised, double-blind, double-dummy, active-control, multicentre trial of 14 weeks in patients with coronary heart disease or multiple cardiovascular risk factors and with primary hypercholesterolaemia not controlled by a starting dose (10mg) of atorvastatin.	
Stein et al.		Am Heart J 2004; 148(3): 447-455.
Protocol 700	Randomised, double-blind, dose-titration multicentre trial of 14 weeks in patients with coronary heart disease or multiple cardiovascular risk factors and with primary hypercholesterolaemia not controlled by a starting dose (20mg) of simvastatin.	
Dobs et al.		J Am Coll Cardiol 2003; 41(6, Suppl. A): 227A-227A.
Protocol 801	Randomised, double-blind, placebo-controlled, multicentre trial of 6 weeks in patients with hypercholesterolaemia and coronary heart disease.	
Brohet et al.		Curr Med Res Opin 2005; 21(4):571-578.
Protocol 802	Randomised, double-blind, placebo-controlled, multicentre trial of 6 weeks in CHD patients with hypercholesterolaemia.	
Farnier et al.		Int J Cardiol 2005; 102(2) 327-332.
Protocol 803 and 804*	Randomised, double-blind, placebo-controlled, multicentre trial of 6 weeks in patients with hypercholesterolaemia and coronary heart disease.	
Cruz-Fernandez et al.		Int J Clin Pract 2005; 59(6) 619-627.
Protocol 1030	Randomised, double-blind, double-dummy, parallel group, multicentre trial of 12 weeks in patients with HoFH.	

Trial	Description	Citations
Gagne C,et al		Circulation 2002; 105(21):2469-2475.
Protocol 2173 and Protocol 2246	Randomised, double-blind, placebo-controlled, multicentre trial of 8 weeks active treatment and 6 weeks reversibility phase in patients with primary hypercholesterolaemia.	
Gagne et al.		Am J Cardiol 2002; 90(10):1084-1091.
EASE Study	Randomised, double-blind, placebo-controlled, multicentre trial of 6 weeks in patients with hypercholesterolaemia.	
Pearson et al.		Mayo Clin Proc 2005; 80(5) 587-595.
Pearson et al.		Am J Geriatric Pharmacotherapy 2005; 3(4) 218-228.

Supportive study: Wierzbicki, AS, Doherty, E, Lumb, PJ, Chik, G, and Crook, MA. Efficacy of ezetimibe in patients with statin resistant and statin intolerant familial hyperlipidemias. Current Medical Research and Opinion 21(3): 333-338, 2005.

8. Results of Trials

For the indication of family history of coronary heart disease or hypertension (Part A):
The results of the analyses showed that there were significantly more patients attaining target LDL-C levels when ezetimibe was added to ongoing statin compared with no addition to statin therapy.

Overall, differences in mean percent change in LDL-C, HDL-C and Total-C from baseline to endpoint across the trials also significantly favoured the addition of ezetimibe to statin monotherapy. The combined estimates for these three lipid parameters were all statistically significant irrespective of the effects model used.

Generally, there were no differences in the percentage of subjects reporting adverse effects between patients treated with statin monotherapy and patients treated with ezetimibe plus a statin.

For the indication of intolerance of high dose statins (Part B):
Results from the supportive study known as Wierzbicki et al, 2005 indicated that the percentage of patients achieving the lipid targets increased from 2.5% to 4% for NCEP-ATP III and from 5.5% to 18% for National Service Framework for Coronary Heart Disease (NSF-CHD).

The difference in the mean percent change from baseline to endpoint for LDL-C, HDL-C and Total C favoured ezetimibe + statin.

Adverse events in the study reported by Wierzbicki et al, 2005 are similar to those reported in the trials in Part A.

9. Clinical Claim

For the indication of family history of coronary heart disease or hypertension (Part A):

The submission claimed that ezetimibe (and ezetimibe + simvastatin) has significant clinical advantages over placebo and is associated with similar or less toxicity.

For the indication of intolerance of high dose statins (Part B):
The submission claimed that ezetimibe (and ezetimibe + simvastatin 10mg) has significant clinical advantages over placebo and is associated with similar or less toxicity. The PBAC considered that this claim was not reasonable. *See Recommendations and Reasons.*

10. Economic Analysis

For the indication of family history of coronary heart disease or hypertension (Part A):
A preliminary economic evaluation was presented. The resources included were drug costs.

Two modelled economic evaluation were presented – one for patients with hypercholesterolaemia and hypertension and the other for patients with hypercholesterolaemia and family history of CHD. The resources included were drug costs and costs of CHD and non-CHD events.

The base case modelled incremental discounted cost/extra life year gained in patients with hypercholesterolaemia and a family history of CHD over a 70-year time horizon was estimated to be in the range $15,000- $45,000.

The base case modelled incremental discounted cost/extra life year gained in patients with hypercholesterolaemia and hypertension over a 70-year time horizon was estimated to be in the range $15,000- $45,000.

For the indication of intolerance of high dose statins (Part B):
A preliminary economic evaluation was presented. The resources included were drug costs.

A modelled economic evaluation was presented. The resources included were drug costs and costs of CHD and non-CHD events.

The base case modelled incremental discounted cost/extra life year gained over a 70-year time horizon was estimated to be in the range $15,000- $45,000.

11. Estimated PBS Usage and Financial Implications

For the indication of family history of coronary heart disease or hypertension (Part A):
The likely number of patients/year was estimated to be in the range 10,000 – 50,000 patients with family history of CHD and in the range 10,000 – 50,000 patients with hypertension in Year 4 of listing.

The financial cost/year to the PBS was estimated to be < $10 million for patients with family history of CHD and < $10 million for patients with hypertension in Year 4.

For the indication of intolerance of high dose statins (Part B):
The likely number of patients/year was estimated to be in the range 10,000 – 50,000 patients in Year 4 of listing. The financial cost/year to the PBS was estimated to be in the range $10 – 30 million in Year 4.

The PBAC considered that the estimates of usage for all indications (Part A and Part B) may result in net costs of $\geq$ $10 million/year in the first year of listing.

12. Recommendation and Reasons

The PBAC recommended extending the authority required listing of ezetimibe to include the treatment of patients with hypertension or a family history of coronary heart disease in patients whose cholesterol levels are inadequately controlled with a statin according to the current ezetimibe PBS restriction definitions of inadequate control. Listing was recommended on a cost effectiveness basis against placebo at the price proposed in the submission.

The PBAC noted that the submission provides evidence that adding ezetimibe to statin therapy lowers low density lipoprotein (LDL) cholesterol. The restriction proposed is also not incompatible with currently allowed access to PBS-subsidised treatment with the statins, and although the absolute risk reduction in some of the patient groups (eg hypertension, early family history of CHD in 2nd degree relatives) covered by the new restriction was considered to be less than for those in the CHD risk equivalent group, this difference is catered for by the differing threshold levels in the General Statement for Lipid-Lowering Drugs.

The PBAC also recommended extending the authority listing of ezetimibe to include the treatment of patients who experience a clinically important product-related adverse event to a statin as defined in the current PBS ezetimibe restriction, but who can continue to take a statin at a dose of 20 mg per day or less (rather than having to discontinue the statin completely as currently). This recommendation was made on the basis of a demonstrated clinical need in a high risk group of patients, where the cost-effectiveness of treatment is established.

The PBAC shared the concerns of the ESC with respect to appropriate comparators and indicated that any future applications for extensions to the listing of ezetimibe either as monotherapy or in combination with simvastatin must be accompanied by a comparison against a therapeutic strategy where the dose of statin is increased or a switch to a more potent (on a mg per mg basis) statin is made, eg. simvastatin 20 mg to atorvastatin 20 mg; atorvastatin 20 mg to rosuvastatin 20 mg. These strategies are increasingly being used in clinical practice and are therefore appropriate additional comparators to placebo.

The Committee further recommended that the requirement that cholesterol level results must be no more than 1 month old at the time of authority application be amended to allow results up to 2 months old to be provided. The PBAC did not consider it clinically appropriate to allow results up to 4 months old to be provided as requested in the sponsor's application. The parallel drawn with the requirement for the thiazolidinediones by the sponsor was also considered to be inappropriate as the four month interval allowed for glycosolated haemoglobin (HbA1c) results reflects the fact that HbA1c levels are slow to change after a therapeutic intervention, and this does not hold true for cholesterol levels.

Recommendation:

EZETIMIBE, tablet 10 mg

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 or
(e) symptomatic cerebrovascular disease or
(f) family history of coronary heart disease or
(g) hypertension
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, a cholesterol level in excess of that threshold 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; 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, a cholesterol level in excess of 4 mmol/L 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 2 months 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 or symptomatic cerebrovascular disease or family history of coronary heart disease or hypertension, whose cholesterol levels were inadequately controlled with a statin, where the patient has previously been issued with an authority prescription for this drug.

Authority required
Patients eligible for PBS-subsidised lipid-lowering medication (according to the criteria set out in the General Statement for Lipid-Lowering Drugs):
(a) where treatment with an HMG CoA reductase inhibitor (statin) is contraindicated; or
(b) where treatment with an HMG CoA reductase inhibitor (statin) must be discontinued or reduced to a dose of 20 mg or less per day, because the patient developed a clinically important product-related adverse event during treatment with a statin.
A clinically important product-related adverse event is defined as follows:

(i) Severe myalgia (muscle symptoms without CK elevation) which is proven to be temporally associated with statin treatment; or
(ii) Myositis (clinically important CK 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.

Authority required
Homozygous sitosterolaemia
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), in combination with an HMG CoA reductase inhibitor (statin).

Maximum quantity: 30
Repeats: 5

Recommendation and Reasons:
The PBAC recommended extending the authority required listing of ezetimibe with simvastatin to include the treatment of patients with hypertension or a family history of coronary heart disease in patients whose cholesterol levels are inadequately controlled with a statin according to the current ezetimibe PBS restriction definitions of inadequate control. Listing was recommended on a cost effectiveness basis against placebo at the price proposed in the submission.

The PBAC noted that the submission provides evidence that adding ezetimibe to statin therapy lowers low density lipoprotein (LDL) cholesterol. The restriction proposed is also not incompatible with currently allowed access to PBS-subsidised treatment with the statins, and although the absolute risk reduction in some of the patient groups (eg hypertension, early family history of CHD in 2nd degree relatives) covered by the new restriction will be much less than for those in the CHD risk equivalent group, this difference is catered for by the differing threshold levels in the General Statement for Lipid-Lowering Drugs.

The PBAC indicated that it would not be prepared to consider any future applications for extensions to the listing of ezetimibe either as monotherapy or in combination with simvastatin unless these applications were accompanied by a comparison against a therapeutic strategy where the dose of the statin is increased or a switch is made to a more potent (on a mg per mg basis) statin, eg. simvastatin 20 mg to atorvastatin 20 mg; atorvastatin 20 mg to rosuvastatin 20 mg. These strategies are increasingly being used in clinical practice and are therefore an appropriate additional comparator to placebo for ezetimibe.

The Committee further recommended that the requirement that cholesterol level results must be no more than 1 month old at the time of authority application be amended to allow results up to 2 months old to be provided. The PBAC did not consider it clinically appropriate to allow results up to 4 months old to be provided as requested in the sponsors application. The

parallel drawn with the thiazolidinediones by the sponsor was also considered to be inappropriate as the four month interval allowed for glycosolated haemoglobin (HbA1c) results reflects the fact that HbA1c levels are slow to change after a therapeutic intervention, and this does not hold true for cholesterol levels.

Recommendation

EZETIMIBE with SIMVASTATIN, tablet, 10 mg – 40 mg and 10 mg – 80 mg

Restriction: Authority required

Initial 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:
(a) coronary heart disease or
(b) diabetes mellitus or
(c) peripheral vascular disease or
(d) heterozygous familial hypercholesterolaemia or
(e) cerebrovascular disease which has become symptomatic or
(f) family history of coronary heart disease or
(g) hypertension

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, a cholesterol level in excess of that threshold 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; 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, a cholesterol level in excess of 4 mmol/L 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 2 months 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 or symptomatic cerebrovascular disease or family history of coronary heart disease or hypertension, 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 ezetimibe and 40 mg or greater of a statin

Patients with homozygous familial hypercholesterolaemia who are ligible 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

Recommendation and Reasons:
NEW STRENGTH
EZETIMIBE with SIMVASTATIN, tablet, 10 mg – 10 mg

The PBAC rejected the application to list a new strength of ezetimibe with simvastatin (10 mg – 10 mg) on the grounds of unclear clinical need, and unnecessary proliferation of dosage forms. There was also a lack of evidence that patients were at a lower risk of side effects with this combination than with a 10 mg dose or higher of a more potent statin. The PBAC noted that a patient was more likely to be switched to a 10 mg dose of a more potent statin than to require the introduction of ezetimibe and that this was clinically appropriate.

However, the PBAC recommended extending the authority listing of ezetimibe to include the treatment of patients who experience a clinically important product-related adverse event to a statin as defined in the current PBS ezetimibe restriction, but who can continue to take a statin at a dose of 20 mg per day or less (rather than having to discontinue the statin completely as currently). This recommendation was made on the basis of a demonstrated clinical need in a high risk group of patients and addressed the situation where a patient was unable to tolerate any statin at a dose of higher than 10 mg.

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

No comment.