

Appendix A – History of PBS listings

AA.1 Ezetimibe tablet, 10mg Ezetrol – June 2003

The sponsor requested an Authority Required listing for the use of ezetimibe:

1. In patients eligible for subsidised lipid lowering medication (according to the Qualifying Criteria in the General Statement for Lipid Lowering Drugs) when HMG-CoA reductase inhibitors (statins) are unsuitable, that is where statin use is contraindicated or the patient developed a clinically important product related adverse event during treatment with a statin, and required discontinuation of all statin treatment. 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 ($> 3 \times \text{ULN}$) during treatment with an HMG CoA reductase inhibitor.
2. Homozygous sitosterolemia.
3. Patients with homozygous familial hypercholesterolaemia who are eligible for subsidised lipid lowering medication, 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.

AA.2 Ezetimibe tablet, 10mg Ezetrol – December 2003

The sponsor requested an Authority Required listing for the use of ezetimibe:

1. For co-administration with 40 mg or greater of a statin in patients with coronary heart disease and/OR diabetes mellitus whose cholesterol levels remain inadequately controlled.

The PBAC recommended listing on the basis of acceptable cost-effectiveness as requested. A particular matter that the PBAC wished to continue to monitor is the extent to which future randomised trials reporting major cardiovascular outcomes where cholesterol therapy is titrated to achieve reductions to target levels demonstrate further reductions in major cardiovascular endpoints beyond that achieved with non-titrated therapy or monotherapy.

2. For initiation by a specialist/consultant physician only: co-administration with statins in patients with Heterozygous Familial Hypercholesterolaemia whose cholesterol levels remain inadequately controlled.

The PBAC rejected the submission because of uncertain extent of clinical benefit and the resulting uncertain cost-effectiveness in the proposed population.

AA.3 Ezetimibe with simvastatin tablet, 10mg – 40mg and 10mg – 80mg Vytorin – March 2005

The submission was for an Authority required listing for (a) treatment of patients whose cholesterol levels are inadequately controlled with 40 mg or more of a statin and who have coronary heart disease or diabetes mellitus; (b) patients with homozygous familial hyperlipidaemia whose cholesterol levels are inadequately controlled with a statin on current lipid lowering treatment.

The PBAC recommended listing with an authority required restriction for patients who have been adequately controlled on a minimum of 3 months of concomitant treatment with PBS-subsidised ezetimibe and PBS-subsidised HMGCoA reductase inhibitor (statin) therapy at a dose of 40 mg per day or more. Consistent with its policy on fixed dose combination products, the PBAC recommended listing on a cost-minimisation basis compared to the sum of the corresponding strengths of the individual components. The PBAC considered that, because there is more than one statin listed on the PBS, but only simvastatin is included in the combination product, it would be more clinically appropriate to stabilise the patient on ezetimibe with the appropriate dose of statin before commencing the combination product.

AA.4 Ezetimibe tablet, 10mg Ezetrol – November 2005

The submission was to extend the current listing to include co-administration with statins in patients with symptomatic cerebrovascular disease (CVD), symptomatic peripheral vascular disease (PVD), or in patients with heterozygous familial hypercholesterolemia (HeFH)

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.

AA.5 Ezetimibe with simvastatin tablet, 10mg – 40mg and 10mg – 80mg Vytorin – November 2005

A request was submitted to extend the recommended listing to include co-administration with statins in patients with symptomatic cerebrovascular disease (CVD), symptomatic peripheral vascular disease (PVD), or in patients with heterozygous familial hypercholesterolemia (HeFH)

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.

AA.6 Ezetimibe tablet, 10mg Ezetrol – November 2006

The submission was to extend authority required indication to allow use in patients with hypertension or a family history of coronary heart disease, whose cholesterol levels are inadequately controlled with a HMG-CoA reductase inhibitor (statin), and to allow use in combination with a low dose of statin in patients with high dose statin intolerance.

The PBAC recommended extending the listing 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, on a cost effectiveness basis against placebo.

The PBAC also recommended extending the listing of the single agent ezetimibe product to include 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, on the basis of a demonstrated clinical need in a high risk group of patients, where cost-effectiveness is established. However, 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, unnecessary proliferation of dosage forms and 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.

AA.7 Ezetimibe with simvastatin tablet, 10mg – 40mg and 10mg – 80mg Vytorin – November 2006

The sponsor submitted a request to extend authority required indication to allow use in patients with hypertension or a family history of coronary heart disease, whose cholesterol levels are inadequately controlled with a HMG-CoA reductase inhibitor (statin).

The PBAC recommended extending the listing 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, on a cost effectiveness basis against placebo.

AA.8 Ezetimibe 10 mg, ezetimibe + simvastatin 10mg/40mg and 10mg/80mg tablets – November 2006

The submission was to request to change current requirement for cholesterol test result to be no more than 1 month old, to no more than 4 months old.

The PBAC agreed to allow the cholesterol test result to be no more than 2 months old at the time of application. 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.

AA.9 Ezetimibe with simvastatin tablet, 10mg – 20mg Vytorin – March 2009

The sponsor's submission was to request an Authority Required (STREAMLINED) listing to include treatment in conjunction with dietary therapy and exercise in patients whose cholesterol levels are inadequately controlled with an HMG CoA reductase inhibitor (statin) at a daily dose of 20 mg or greater and who meet the criteria of the General Statement for Lipid-Lowering Drugs Prescribed as Pharmaceutical Benefits.

The PBAC rejected the application on the basis of a lack of clinical need, given the availability of statins to provide a similar health benefit, that in terms of a cost-effectiveness evaluation the listing would provide currently available benefits at a higher cost, and the listing would place an additional significant financial burden on the PBS.

AA.10 Ezetimibe tablet, 10mg Ezetrol – November 2009

Request to change the current Authority Required (STREAMLINED) listings to Restricted Benefit.

The submission was rejected as the PBAC considered the more restrictive classification remained appropriate for these products.

AA.11 Ezetimibe tablet, 10mg Ezetrol – November 2010

Requests amending the current Authority Required (Streamlined) listing definition of 'inadequate control' to allow the addition of ezetimibe to 20 mg of rosuvastatin or atorvastatin as opposed to the current "...40 mg or above of a statin".

The PBAC recommended that the restriction for ezetimibe be amended to incorporate wording that does not specify a particular dose of a statin be attempted to achieve an appropriate lowering of cholesterol, rather that the wording should stipulate a three month trial with the maximum tolerated dose of a statin.

This option allows ezetimibe to be added as clinically appropriate while continuing to support up-titration of statins as the first line treatment of hypercholesterolaemia.

AA.12 Ezetimibe with simvastatin tablet, 10mg – 10mg, 10mg – 20mg Vytorin – July 2012

The submission was to request an extension to the listing of the 10 mg-10 mg and 10 mg-20 mg strengths to include the additional indication of 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 meet certain criteria.

The PBAC recommended the extension of listing as requested in order to remove inequities for those patients whose maximum tolerated dose of simvastatin was 10 mg or 20 mg per day.

AA.13 Ezetimibe + atorvastatin, 10 / 10mg, 20 / 10mg, 40 / 10mg, 80 / 10mg Atozet co-pack – July 2013

A re-submission for an Authority required (Streamlined) listing for hypercholesterolaemia in patients meeting certain criteria.

The PBAC recommended Authority required (Streamlined) listing of ezetimibe and atorvastatin 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, on a cost-minimisation basis with the corresponding doses of the components (ezetimibe and atorvastatin) given concomitantly.

