PUBLIC SUMMARY DOCUMENT

Product: Sibutramine hydrochloride, capsules, 10 mg and 15 mg, Reductil/Ectiva®

Sponsor: Abbott Australasia

Date of PBAC Consideration: November 2006

1. Purpose of Application

The resubmission requested an authority required listing for the management of severe obesity associated with multiple risk factors.

2. Background

At the March 2006 meeting, the PBAC rejected a submission for sibutramine for a Restricted Benefit listing on the Pharmaceutical Benefits Scheme (PBS) for the treatment of severe obesity (body mass index (BMI) $\geq$ 35 kg/m^2) in the presence of two or more of the following risk factors: Type 2 diabetes, hypertension, high triglycerides or low high density lipoproteins, because of doubts about the extent of clinical benefit, the resulting uncertain cost-effectiveness and a high potential for use outside the restriction.

3. Registration Status

Sibutramine is TGA approved for the management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced calorie diet. Sibutramine is recommended for obese patients with an initial body mass index (BMI) greater than or equal to 30 kg per square metre or greater than or equal to 27 kg per square metre in the presence of other obesity-related risk factors (e.g. diabetes, dyslipidaemia, hypertension). Sibutramine may only be prescribed to patients who have not adequately responded to an appropriate weight-reducing regimen alone (hypocaloric diet and/or exercise) i.e. patients who have difficulty achieving or maintaining greater than 5% weight loss within 3 months.

4. Listing Requested and PBAC's View

Authority required

For the treatment, in conjunction with a reduced caloric diet, of severe obesity (BMI $\geq$ 35 kg/m^2) in adults between 18 and 65 years of age who:

(a) are normotensive patients with adequately controlled hypertension (< 145/90 mmHg); AND
(b) have not adequately responded to an appropriate weight reducing regimen alone (hypocaloric diet and/or exercise); AND
(c) have 2 or more of the following risk factors:
    (i) Type 2 diabetes; OR
    (ii) Triglycerides > 150 mg/dL (> 1.695 mmol/L); OR
    (iii) HDL < 50 mg/dL (< 1.295 mmol/L) for females or < 40 mg/dL (<1.036 mmol/L) for males

Initial treatment in diabetic patients

Diabetic patients should receive an initial six months treatment with sibutramine. A weight review must be undertaken at 6 months and treatment must be discontinued for diabetic patients whose weight loss within six months after starting therapy has been less than 5% of

their initial bodyweight. Patients are allowed to receive one course of initial treatment every 12 months.

Initial treatment in non-diabetic patients
Non-diabetic patients should receive an initial 3 months of treatment. A weight review must be undertaken at 3 months and treatment must be discontinued in non-diabetic patients whose weight loss within 3 months after starting therapy has been less than 5% of their initial bodyweight. Patients are allowed to receive one course of initial treatment every 12 months.

Continuing treatment
Continuing treatment in patients who initially responded adequately to therapy as outlined above (i.e. a greater than 5% loss in weight after 3 months in non-diabetics and after 6 months in diabetics). Total treatment will not exceed 24 months from initial application.

See Recommendation and Reasons for the PBAC's view.

5. Clinical Place for the Proposed Therapy

In conjunction with diet and/or exercise, sibutramine provides a treatment option for severely obese patients with or at high risk of developing related co-morbidities to lose weight and initiate or increase exercise.

6. Comparator

The submission nominated standard medical management consisting of lifestyle modification (specifically, a reduced calorie diet and/or exercise) which was accepted by the PBAC as the appropriate comparator.

7. Clinical Trials

Four new trials in addition to those of the previous submission were included in the meta-analysis, which now included 44 trials. One new study was included as supportive evidence. No new patient level data had become available since the March 2006 submission. The subgroup analysis of patient level data including patients who would be eligible for sibutramine under the requested restriction had been revised to reflect changes in the requested restriction.

The trials included in the submission had been published as follows:

Trial/First author	Protocol title	Publication citation
Bauer C et al	Effect of sibutramine and of cognitive-behavioural weight loss therapy in obesity and subclinical binge eating disorder.	Diabetes, Obesity and Metabolism 2006; 8:289-295.
de Simone G et al	Effects of sibutramine-induced weight loss on cardiovascular system in obese subjects.	Nutrition Metabolism and Cardiovascular Diseases 2005; 15(1):24-30
Wadden TA et al	Randomized trial of lifestyle modification and pharmacotherapy for obesity.	New England Journal of Medicine 2005; 353(20):2,111-2,120.
Wang TF et al	Effects of sibutramine in overweight, poorly controlled Chinese female type 2 diabetic patients: a randomised, double-blind, placebo-controlled study.	International Journal of Clinical Practice 2005; 59(7):746-750.
Mathus-Vliegen EM, Balance	Long-term maintenance of weight loss with sibutramine in a GP setting	European Journal of Clinical Nutrition 2005; 59(Suppl 1):S31-38; discussion S39.

Trial/First author	Protocol title	Publication citation
Study Group.	following a specialist guided very-low-calorie diet: a double-blind, placebo-controlled, parallel group study.	
Redmon JB et al	Two-year outcome of a combination of weight loss therapies for type 2 diabetes.	Diabetes Care 2005; 28(6):1,311-1,315. [Additional publication to Redmon (2003).]
Malone DC et al	Cost-effectiveness of sibutramine in the LOSE Weight Study: evaluating the role of pharmacologic weight-loss therapy within a weight management program.	Journal of Managed Care Pharmacy 2005; 11(6):458-468. [Additional publication to Porter (2004).]

8. Results of Trials

Statistically significantly more patients treated with sibutramine achieved weight loss of ≥5% and ≥10% of their body weight, compared with placebo-treated patients. Patients on sibutramine also achieved numerically small, but statistically significant reductions in BMI, weight and waist circumference compared with placebo-treated patients.

The results of the patient level analysis support the results of the meta-analysis. An additional analysis of the weight loss distribution of patients in the overall patient analysis and the eligible patient analysis showed that significantly more sibutramine-treated patients lost ≥10% and ≥15% of body weight, compared with placebo-treated patients. However, the difference between the proportion of patients losing ≥15% of their body weight was small (<5% in both populations). *See Recommendations and Reasons.*

9. Clinical Claim

The submission claimed that sibutramine had significant advantages in effectiveness over placebo for standard medical management but has more toxicity.

The PBAC considered that this description might be reasonable, however, the clinical importance of the treatment benefit must be balanced against the potential for higher blood pressure, pulse rate and other adverse events, particularly in the absence of long-term data on the maintenance of weight loss and safety. *See Recommendations and Reasons.*

10. Economic Analysis

An updated preliminary economic evaluation was presented, incorporating the reduced price per pack of sibutramine and the updated 'eligible population' analysis, based on changes to the requested PBS restriction.

The trial-based incremental cost/extra patient with adequate (≥5%) weight loss at 6 months was estimated to be < $15,000 for the total population; and < $15,000 for the eligible patient population.

An updated modelled economic evaluation was presented. The model in the re-submission:

- incorporated the reduced price of sibutramine;
- removed the United Kingdom Prospective Diabetic Study (UKPDS) risk equations so that the risk of diabetic patients for amputation, blindness, renal failure or diabetes-related mortality was not modelled;
- updated the patient population according to the revised requested restriction; and
- updated some cost variables where more recent data have become available.

The base case modelled incremental discounted cost/Quality Adjusted Life Year (QALY) gained was estimated to be in the range $15,000- $45,000.

11. Estimated PBS Usage and Financial Implications

The likely number of patients/year was estimated to be in the range 10,000 – 50,000 in the third year of listing.

The financial cost/year to the PBS was estimated to be in the range $30 – $60 million in Year 3.

12. Recommendation and Reasons

The PBAC accepted standard medical management consisting of lifestyle modification (specifically, a reduced calorie diet and/or exercise) as the appropriate comparator noting the sponsor's comment in the Pre-Sub-Committee response and in the submission, that surgical interventions such as gastric banding is, in present day practice, a third line option after diet, exercise and pharmacotherapy have failed. This was accepted as reasonable by the PBAC.

From a general public health perspective, the PBAC expressed a view that the causes of obesity are complex and involve societal-level factors that are difficult to change, and any pharmacological therapy aimed at treating patients with extreme BMI will contribute only marginally to a wider community solution for obesity.

The PBAC noted that this resubmission addressed several concerns raised with the previous submission.

The requested restriction for the now Authority Required listing, reflected that previously proposed by the ESC and included initiation and continuation rules. The PBAC noted that the Pre-Sub-Committee Response clarified that the intent of the restriction wording was not to limit patient access to only one continuous treatment of 24 months per lifetime. Rather, the intent was that at the end of 24 months of treatment, patients would have to requalify for further treatment. The wording of the restriction was also changed from that originally proposed, such that non-responders would be eligible for subsidised sibutramine after 24 months (instead of 12 months), to be consistent with the wording for eligibility for continuing treatment.

The concern relating to whether ≥5% weight loss, was sufficient weight loss in the very obese population as targeted in the requested restriction, particularly in the absence of evidence of long-term benefit was addressed in the re-submission which drew the Committee's attention to the NHMRC guidelines supporting a weight loss of 5% as a realistic target associated with significant clinical benefit. Despite this, the PBAC considered that the inclusion of the four additional trials in the meta-analysis did not demonstrate a magnitude of weight loss greater than seen in the previous submission, and remained unconvinced about what would be the quantifiable change in the more clinically meaningful cardiovascular outcomes being predicted by a ≥5% reduction in weight in severely obese patients.

Although captured in the economic model, the PBAC noted that the evidence presented showed that systolic blood pressure, diastolic blood pressure and pulse rate were all statistically significantly higher in sibutramine-treated patients and therefore remained concerned, as in the previous submission, that the clinical importance of the treatment effects

demonstrated on physiological variables need to be balanced against the potential for higher blood pressure, pulse rate and other adverse events.

The model in the previous submission which incorporated UKPDS risk equations, and was considered to carry the risk of overestimating Australian diabetes-related mortality rates by 2-3 times, was addressed in the resubmission with the removal of these equations from the base case of the model.

The total cost to the PBS and the large potential for use outside the restriction was addressed through a combination of a price reduction, and a more restrictive listing as noted above. The sponsor would also be willing to enter into a risk sharing arrangement. The PBAC noted the Quality Use of Medicines Program outlined by the sponsor during the hearing including setting up a register of patients receiving treatment for monitoring purposes. The sponsor proposed at the hearing that any risk sharing cap to be negotiated, would take into account the cost of setting up and running the Quality Use of Medicines Program and the register, which would be borne initially by the sponsor as a cost-offset. The Committee considered that setting up a register as proposed at the hearing would raise critical privacy and data linkage issues, which are not resolved and would need to be addressed in the future.

The PBAC considered that there were several problems relating to the construction of the modelled economic evaluation which relied on inputs not necessarily relevant to the treatment population targeted by the requested restriction, and this gave rise to uncertainties in the cost-effectiveness estimates.

The model assumed patients who do not respond within six months receive no further sibutramine therapy, whereas the requested restriction allowed patients to retry therapy every 24 months, irrespective of response. The Pre-Sub-Committee Response provided a further sensitivity analysis which allowed non-responders to re-try sibutramine for 3-6 months of every treatment cycle resulting in an ICER in the range $45,000 - $75,000 per QALY.

The applicability of cardiovascular risk equations derived from epidemiological cohorts of patients, such as the Framingham risk equation used in this model, to patients who have achieved the same weights through pharmacotherapy, was also of concern. For example, weight loss of 10kgs achieved by taking a drug is unlikely to have the same impact on cardiovascular outcomes than if the same weight loss would have been achieved by an increase in physical activity.

The model for responders to sibutramine therapy is based on 2.5 year treatment cycle which has three periods: an initial six-months of weight loss, 18 months of weight maintenance, followed by a six months break from the drug in which sibutramine patients regain weight at the same rate as placebo-treated patients. Once it is re-started, the benefit of a treatment effect is applied again, but it is lower than in the initial cycle. The effect of fluctuating weight on risk factors is not known. Also there would be additional costs of sibutramine if that 6 month break did not occur, and this adds to the uncertainty of the resulting cost-effectiveness ratios.

The PBAC accepted the further advice of the ESC regarding the fact that there are no data beyond two years to support the assumptions regarding weight loss in the subsequent cycles. In addition, the model assumes a natural weight gain, however, the study (Heitmann &

Garby, 1999) nominated to support the extent of gain assumed in the model was not conducted in patients with a BMI ≥35kg/m2 at baseline. It is not clear that the results from this study are generalisable to the population in the model. The PBAC also remained concerned that the differences in utilities between patients with and without diabetes used in the model are likely to be due to the different methodologies used to derive utilities.

Overall, the model was considered to overestimate the potential benefits of sibutramine therapy. The predicted incremental cost per Quality Adjusted Life year (QALY) was considered to be high when compared to other lifestyle modification options, and highly uncertain due to the use of surrogate outcomes and remaining inconsistencies between the model inputs and the proposed listing.

The PBAC rejected the submission because of doubts about the extent and duration of clinical benefit, and the resulting uncertain cost-effectiveness.

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 agrees with the PBAC that the causes of obesity are complex. Nevertheless, the sponsor believes that pharmacotherapy has an important role to play as a part of an integrated programme to reduce weight and the associated risk of diabetes and cardiovascular disease. We will continue to work with the PBAC and other key stakeholders to support the role of sibutramine as an important pharmacological therapy in the treatment of obesity in the Australian community.