PUBLIC SUMMARY DOCUMENT
Product: Sibutramine hydrochloride, capsules, 10 mg and 15 mg, Reductil®/Ectiva®
Sponsor: Abbott Australasia Pty Ltd
Date of PBAC Consideration: March 2008

1. Purpose of Application

The application sought an Authority Required listing for the management of type 2 diabetics with obesity and abnormalities in high density lipoproteins (HDL) and triglycerides.

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) ≥ 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. There were doubts about the extent of clinical benefit, the resulting uncertain cost-effectiveness and a high potential for use outside the restriction.

At the November 2006 meeting the PBAC rejected a re-submission for sibutramine for an Authority Required listing on the PBS for the management of severe obesity associated with two or more of the following risk factors: Type 2 diabetes, hypertension, high triglycerides or low high density lipoproteins. This was due to doubts about the extent and duration of clinical benefit, and the resulting uncertain cost-effectiveness.

At the July 2007 PBAC meeting the Committee rejected a re-submission presenting a revised predicted incremental cost per Quality-Adjusted Life-Year (QALY). The PBAC rejected the submission based on uncertainty about the extent of clinical benefit and uncertain cost-effectiveness.

3. Registration Status

Sibutramine was registered by the TGA on 1 November 2001. It is indicated 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. BMI is calculated by taking the patient's weight, in kg, and dividing by the patient's height, in metres, squared. Sibutramine is not intended for use in obese children under 18 years of age as safety and efficacy in this population has not been established. Sibutramine is not intended for use in elderly patients over 65 years of age as safety and efficacy in this population has not been established.

4. Listing Requested and PBAC's View

Authority required:

For the treatment, in conjunction with a reduced caloric diet, of type 2 diabetic adults between 18 and 65 years of age with obesity (BMI ≥ 30 kg/m2) who:

• are normotensive patients with adequately controlled hypertension (< 145/90 mmHg) AND

• have not adequately responded to an appropriate weight-reducing regimen alone (hypocaloric diet and/or exercise) AND
• have either:
1. Triglycerides > 150 mg/dL (>1.695 mmol/L) OR
2. HDL < 50 mg/dL (<1.295 mmol/L) for females or < 40 mg/dL (<1.036 mmol/L) for males
• have an obesity management plan developed consistent with the Chronic Disease Management items on the Medicare Benefits Schedule.

Initial treatment:
Patients should receive an initial six months of treatment with Reductil. A weight review must be undertaken at six months and treatment must be discontinued for 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 24 months.

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

See Recommendation and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

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

6. Comparator

The submission nominated lifestyle modification (specifically, a reduced calorie diet and/or exercise) as the main comparator. This was accepted by the PBAC as appropriate.

7. Clinical Trials

The basis of the submission was:

- a meta-analysis of 10 direct randomised comparative trials which were part of the evidence base for the July 2006 re-submission comparing sibutramine (plus lifestyle modification) and placebo plus lifestyle modification; and
- a *post hoc* patient level analysis using those trials enrolling type II diabetics for whom patient level data was available (i.e. SB3051, SB5075, SB5078, SB6085 and SB6087).

Trial details are included in the March 2006 and November 2006 Public Summary Documents.

8. Results of Trials

Individual Patient Data meta-analysis

Significantly, more patients achieved ≥5% weight loss on sibutramine plus lifestyle modification versus lifestyle modification alone in the general obese population, the obese diabetic population, and the PBS eligible population. The results are presented in the table below.

Proportion of patients achieving ≥5% loss of body weight in the general obese population [a] (July 2006), the obese diabetic population [b] and the PBS eligible population[c]

No of trials	SIB + LM pts	Placebo + LM pts	Risk difference (95% CI)	Risk ratio (95% CI)
Patient-level analysis-overall general obese population, July 2006 re-submission (N = 3299)				
23	952/1846 (51.6%)	324/1453 (22.3%)	0.29 (0.26, 0.32)	2.31 (2.08, 2.57)
Patient-level analysis-obese diabetic population, November 2007 re-submission (N=629)				
5	154/317 (48.6%)	53/312 (17.0%)	0.32 (0.25, 0.39)	2.86 (2.18, 3.75)
Patient-level analysis-PBS eligible population, November 2007 re-submission (N=167)				
5	37/81 (45.7%)	14/86 (16.3%)	0.29 (0.16, 0.43)	2.81(1.64, 4.79)

Notes: [a] data included for comparison; [b] all key trial populations in current re-submission; [c] resulting population after applying PBS eligibility criteria to the key trial populations in the current resubmission; SIB = sibutramine; LM = lifestyle modification.

The results for patients achieving ≥10% loss of body weight are presented in the table below.

Proportion of patients achieving ≥10% loss of body weight in the obese diabetic population [a] and the PBS eligible population[b]

No of trials	SIB + LM pts	Placebo + LM pts	Risk difference (95% CI)	Risk ratio (95% CI)
Patient-level analysis-obese diabetic population, November 2007 re-submission (N=629)				
5	53/317 (17%)	12/312 (4%)	0.13 (0.08, 0.18)	4.34 (2.37, 7.97)
Patient-level analysis-PBS eligible population, November 2007 re-submission (N=167)				
5	11/81 (13.5%)	3/86 (3.5%)	0.10 (0.02, 0.19)	3.89 (1.12, 13.45)

Notes: [a] all key trial populations in current re-submission; [b] resulting population after applying PBS eligibility criteria to the key trial populations in the current resubmission; SIB = sibutramine; LM = lifestyle modification.

Significantly, more patients achieved ≥10% weight loss on sibutramine plus lifestyle modification versus lifestyle modification alone in both the obese diabetic and PBS eligible populations. The PBAC was advised the results should be interpreted in the context that this conclusion was based on post hoc subgroup analyses.

In the PBS eligible population, significantly more patients on sibutramine plus lifestyle modification lost 5-10% and 10-15% of initial body weight, compared to patients on placebo plus lifestyle modification. There was no difference between the groups in the proportion of patients losing ≥15% of their weight.

The re-submission stated that significant individual responses in these data were concealed by small mean differences. However, given that only 13.5% of sibutramine treated patients achieved a weight loss of more than 10% and even fewer (2.4% and 1.2% of patients on sibutramine and placebo respectively) achieved weight lost greater than 15%, the PBAC considered that individual responses representing substantial weight loss were uncommon,

and not significantly more likely with sibutramine than with placebo. However, it was acknowledged that the introduction of a continuation rule (loss of 5% of body weight at 6 months) was intended to address this uncertainty about the magnitude of the clinical benefit across of the population.

Trial Meta-analysis

The results for weight, lipid, cardiovascular and diabetes related changes are shown in the table below.

Weight, lipid, cardiovascular and diabetes related changes

Variable	No of trials (N=10)	Mean change from baseline to endpoint [95% CI]		Weighted mean difference [95% CI]	p-value/ I^2 for heterogeneity
		SIB + LM pts (N)	Placebo + LM pts (N)		
Change in weight					
BMI (kg/m^2)	8	–1.75 [–1.93, –1.57] (420)	–0.38 [–0.53, –0.24] (415)	–1.36 [–1.77, –0.96][a,b]	< 0.00001/ **72.2%**
Weight (kg)	8	–4.68 [–5.14, –4.23] (482)	–1.20 [–1.60, –0.81] (472)	–3.48 [–4.55, –2.41] [a]	< 0.00001/ **72.5%**
Weight (%)	10	–5.21 [–5.68, –4.74] (384)	–1.56 [–1.98, –1.15] (379)	–3.65 [–4.79, –2.51] [a]	< 0.00001/ **72.5%**
Waist circum. (cm)	7	–5.05 [–5.68, –4.52] (384)	–1.73 [–2.32, –1.14] (379)	–3.32 [–4.69, –1.96] [a]	< 0.00001/ **67%**
Change in lipid variables					
TC (mmol/L)	10	-0.21 [-0.28, -0.14] (480)	-0.05 [-0.11, 0.01] (468)	-0.16 [-0.31, -0.01][a]	0.04/ **65%**
TC (%)	3	1.68 [-0.02, 3.39] (246)	1.55 [-0.14, 3.24] (247)	0.13 [-0.27, 2.53] [c]	0.91/ 0%
HDL (mmol/L)	8	0.05 [0.03, 0.07] (425)	-0.01 [-0.03, 0.01] (414)	0.06 [0.04, 0.09] [c]	< 0.00001/ 0%
HDL (%)	3	8.33 [5.86, 10.8] (240)	1.20 [-1.50, 3.90] (240)	7.13 [3.46, 10.8] [c]	0.000/ 22%
LDL (mmol/L)	8	-0.08 [-0.14, -0.02] (422)	0.04 [-0.02, 0.11] (406)	-0.13 [-0.25, 0.00] [a]	0.05/ **49.2%**
LDL (%)	3	4.07 [1.41, 6.73] (238)	4.93 [2.14, 7.72] (235)	-0.86 [-4.70, 2.98] [c]	0.66/ 0%
Trig (mmol/L)	9	-0.21 [-0.30, -0.13] (462)	-0.08 [-0.15, -0.01] (451)	-0.13 [-0.24, -0.02] [a]	0.017/ 16%
Trig[b]. (%)	3	-2.24 [-7.56, 3.-7] (246)	5.48 [0.37, 10.6] (247)	-7.73 [-15.1, -0.38][c]	0.039/ 0%
Cardiovascular variables					
SBP (mmHg)	7	1.03 [-0.55, 2.61] (363)	-0.29 [-1.78, 1.19] (360)	1.33 [-0.84, 3.50] [c]	0.23/ 0%
DBP (mmHg)	7	1.52 [0.64, 2.39] (363)	-0.17 [-1.13, 0.79] (360)	1.69 [0.39, 2.98] [c]	0.01/ 0%
Pulse (bpm)	8	3.61 [2.62, 4.59] (408)	0.38 [-0.54, 1.30] (403)	3.23 [1.08, 5.38] [a]	0.003/ **61%**
Diabetes related variables					
Glucose (mmol/L)	8	-0.75 [-0.90, -0.61] (405)	-0.40 [-0.61, -0.19] (399)	-0.35 [-0.60, -0.10] [a]	0.006/ 0%
HbA1c (%)	9	-0.45 [-0.55, -0.35] (435)	-0.14 [-0.24, -0.04] (427)	-0.31 [-0.45, -0.16] [c]	< 0.0001/ 6%

Notes: [a]random effects; [b]changed by the Sponsor from (-1.77, -1.40) to (-1.77, -0.96) after request for the forest plots; Bolded I^2 demonstrate significant statistical heterogeneity; [c] fixed effects; % = percent of baseline; SIB = sibutramine; LM = lifestyle modification; BMI = body mass index; TC = total cholesterol; HDL = high density lipoprotein; LDL = low density lipoprotein; Trig = triglycerides.

Sibutramine plus lifestyle modification was associated with numerically small but a statistically significant greater reduction in body mass index, weight and waist circumference compared with placebo plus lifestyle modification. Sibutramine plus lifestyle modification resulted in increased blood pressure and pulse rate relative to placebo plus lifestyle modification. There was significant heterogeneity between the direct trials in terms of sibutramine treatment duration and the definitions of low calorie diet and exercise.

The PBAC noted that the recent literature on weight loss in obesity states, "intentional weight loss can improve or prevent many of the obesity-related risk factors for CHD (i.e. insulin resistance and type 2 DM, dyslipidaemia, hypertension and inflammation). Moreover, these metabolic benefits are often found after only modest weight loss (~5% of initial weight) and continue to improve in a monotonic fashion with increasing weight loss." (Klein et al, Circulation 2004; 110:2952-2967).

However, in this re-submission, as in previous submissions for sibutramine, no direct data were submitted to indicate any benefit in terms of cardiovascular outcomes. There was a reasonable cause for concern that the weight loss achieved with sibutramine may be counterbalanced by the effects on blood pressure and pulse rate in terms of cardiovascular risk.

No new toxicity data were presented in the re-submission. The toxicity data from the March 2006 submission noted that treatment with sibutramine was associated with significant increases in systolic and diastolic blood pressure and increases in pulse rate and sibutramine-treated patients experienced more headaches, constipation and dry mouth compared to placebo-treated patients. Relevant data that examine the comparative safety profiles of sibutramine and placebo, from a pool of 46 sibutramine trials, were extracted during the evaluation of the re-submission. The results are summarised in the table below.

Comparative safety data from a pooled analysis of 46 sibutramine versus placebo trials.

Number of trials (N=46)	**Sibutramine plus LM (N=1828)**	**Placebo plus LM (N=1437)**	**p-value**
Overall adverse events by body system[a]			
Cardiovascular	204 (11.2%)	109 (7.5%)	0.0006
Digestive	582 (31.8%)	324 (22.5%)	0.0001
Endocrine	3 (0.2%)	2 (0.1%)	0.0006
Lymphatic	25(1.4%)	17 (1.2%)	0.64
Metabolic and nutritional	116 (6.3%)	93 (6.5%)	0.88
Musculoskeletal	186 (10.2%)	115 (8.0%)	0.033
Nervous system	637 (34.8%)	283 (19.7%)	0.0001
Respiratory	350 (19.1%)	248 (17.3%)	0.17
Skin and appendages	235 (12.9%)	123 (8.6%)	0.0001
Special senses	127 (6.9%)	55 (3.8%)	0.0001
Genito-urinary	224 (12.3%)	134 (9.3%)	0.0001
Overall cardiovascular events stratified[a]	**Sibutramine (N=1828)**	**Placebo (N=1437)**	**p-value**
Stroke/cerebral ischemia	2 (0.1%)	3 (0.2%)	0.47
MI	0 (0.0%)	0(0.0%)	0.47
Migraine	31 (1.7%)	22 (1.5%)	0.28
Hypertension	30 (1.6%)	17 (1.2%)	0.71
Palpitations	35 (1.9%)	8 (0.6%)	0.0007

Tachycardia	39 (2.1%)	7 (0.5%)	0.0001
Vasodilatation (flushes)	30 (1.6%)	10 (0.7%)	0.015
Syncope	8 (0.4%)	6 (0.4%)	0.93
Peripheral Vascular disease	25 (1.4%)	7 (0.5)	0.011

Notes: [a] not specified; LM = lifestyle modification.

The PBAC noted the statistical tests of significance presented with the data provided little, if any, useful information on the clinical importance of differences in the comparative safety profiles of sibutramine and placebo. The data suggested that there may be clinically important differences in adverse events of the cardiovascular, digestive and nervous systems with sibutramine usage. Although the event rates appeared low (possibly because of short follow up periods of the majority of the trials), the high baseline risk among the intended population for listing, obese type 2 diabetics, raised concerns regarding an increased cardiovascular risk due to sibutramine treatment that might not be offset by a modest weight loss. Of note was the fourfold increase in the risk of tachycardia subsequent to treatment with sibutramine compared with placebo.

9. Clinical Claim

The submission claimed that sibutramine plus lifestyle modification has significant advantages in effectiveness over placebo plus lifestyle modification but has more toxicity.

See Recommendation and Reasons for PBAC's view.

10. Economic Analysis

An updated modelled economic evaluation was presented. The model in the re-submission incorporated the reduced price of sibutramine, re-introduced the UKPDS risk equations (in addition to the Framingham risk equations) where the diabetes-related mortality is halved (following advice from the investigators of the Australian FIELD trial), updated the patient population according to the revised requested PBS restriction, and introduced maintenance costs for relevant diabetes-related complications.

The structure of the model remained the same as in the previous submissions except that the non-diabetes arm of previous models was now redundant given that listing was requested for obese type 2 diabetics. A sensitivity analysis was conducted around the UKPDS mortality factor.

The incremental cost per quality-adjusted life-year (QALY) gained was estimated in the re-submission to be in the range of $45,000 to $75,000 when the UKPDS mortality factor was assumed zero, and between $15,000 and $45,000 when the UKPDS mortality rate is halved.

11. Estimated PBS Usage and Financial Implications

The re-submission estimated the likely number of patients per year to be between 10,000 and 50,000 in Year 3.

The submission estimated the financial cost per year to the PBS to be between $10 - $30 million in the second year of listing.

12. Recommendation and Reasons

The PBAC noted the sponsor had agreed with the Restriction Working Group wording for the restriction that only one course of initial treatment be authorised were the drug to be recommended for listing.

The PBAC noted that in the PBS eligible population, significantly more patients on sibutramine plus lifestyle modification lost 5-10% and 10-15% of initial body weight, compared to patients on placebo plus lifestyle modification. There was no difference between the groups in the proportion of patients losing ≥15% of their weight. It was acknowledged that the introduction of a continuation rule (loss of 5% body weight at 6 months) is intended to address the uncertainty about the magnitude of the clinical benefit across the population.

The PBAC also noted that sibutramine plus lifestyle modification was associated with a numerically small but statistically significant greater reduction in body mass index, weight and waist circumference compared with placebo plus lifestyle modification. Sibutramine plus lifestyle modification resulted in increased blood pressure and pulse rate relative to placebo plus lifestyle modification.

However, as in previous submissions for sibutramine, no direct data were submitted to indicate any benefit in terms of cardiovascular outcomes. The PBAC considered there is a reasonable cause for concern that the weight loss achieved with sibutramine may be counterbalanced by the effects on blood pressure and pulse rate in terms of cardiovascular risk.

Also of concern was the lack of data on the sustainability of weight loss over time. The economic modelling continues to be hampered by the limitations of the available data to reasonably predict long term weight changes for the treatment arm, as there were no data beyond two years to support the assumptions regarding weight loss in the subsequent cycles of the model.

The Committee noted that the structure of the economic model remained the same and a sensitivity analysis was conducted around the UKPDS mortality factor. The ICER per extra QALY gained was between $45,000 and $75,000 when the UKPDS mortality factor is assumed zero as compared to the base case ICER per extra QALY gained of between $15,000 and $45,000 when the UKPDS mortality rate is halved.

The Committee noted the recent literature on weight loss in obesity states, "intentional weight loss can improve or prevent many of the obesity-related risk factors for CHD (i.e. insulin resistance and type 2 DM, dyslipidaemia, hypertension and inflammation). Moreover, these metabolic benefits are often found after only modest weight loss (~5% of initial weight) and continue to improve in a monotonic fashion with increasing weight loss." (Klein et al, Circulation 2004; 110:2952-2967).

Nevertheless, given that sibutramine has been approved for weight loss in the US for over 10 years, it is disappointing that direct patient-relevant clinical outcome data are not available. The PBAC was encouraged that such data are to be forthcoming soon. The Committee noted the Sibutramine Cardiovascular Outcome trial (SCOUT) was due to report in 2008. The primary endpoint of the trial will include a composite of myocardial infarction,

stroke, resuscitated cardiac arrest, and cardiovascular death, which the members anticipated, will provide information regarding whether or not the blood pressure and HR effects of sibutramine counter any of the impact of weight loss and inform the cost effectiveness assessment.

The PBAC rejected the application because although the current submission has achieved a greater focusing of the restriction and reduced the overall cost to the PBS, it has provided no further progress in terms of answering the PBAC's previous doubts about the extent of clinical benefit, and hence 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 thanks the PBAC for their consideration.