Public Summary Document

Product:	Sibutramine hydrochloride, capsules, 10 mg and 15 mg, Reductil/Ectiva®
Sponsor:	Abbott Australasia
Date of PBAC Consideration:	March 2006

1. Purpose of Application

The submission sought 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.

BMI is calculated by taking the patient's weight, in kg, and dividing by the patients height, in metres, squared.

2. Background

This drug had not previously been considered by the PBAC.

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. 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

Restricted Benefit:

For the treatment of severe obesity (BMI ≥ 35 kg/m^2) with two or more of the following risk factors:

- Type 2 diabetes
- Adequately controlled hypertension (< 145/90)
- Triglycerides > 150 mg/dL
- HDL < 50 mg/dL (females) or < 40 mg/dL (males)

See Recommendations and Reasons for PBAC's View.

5. Clinical Place for the Proposed Therapy

Sibutramine provides an alternative for obese patients with other risk factors who have exhausted all other options to lose weight.

6. Comparator

The submission nominated placebo for standard medical management as the comparator. Standard medical management consists of lifestyle modification; specifically a reduced calorie diet and/or exercise. The PBAC did not accept that placebo for standard medical management was the only appropriate comparator. *See Recommendations and Reasons.*

7. Clinical Trials

The submission presented data from 42 randomised controlled trials of sibutramine versus placebo, investigating weight loss in overweight or obese individuals with a range of co-morbidities and risk factors and patient level analyses for 23 of the double-blind trials as primary evidence of efficacy and safety. In addition the submission presented supportive data from 3 double-blind randomised controlled trials of sibutramine vs placebo investigating the long-term maintenance of weight loss in overweight or obese individuals.

The trials which had been published at the time of submission are as follows:

Trial/First author	Protocol/Publication title	Publication citation
Appolinario (2003)	Appolinario JC et al. A randomized, double-blind, placebo-controlled study of sibutramine in the treatment of binge-eating disorder.	Archives of General Psychiatry 2003; 60:1109-16.
Ballard (2001)	Abstract: Ballard RD et al. Efficacy of sibutramine for promoting weight loss in the treatment of obstructive sleep apnea.	International Journal of Obesity 2001; 25(Suppl 2):S109
BPI 852	Trial BPI 852: A multicenter double-blind, repeated dose placebo-controlled, parallel group dose-ranging study to evaluate the weight-reducing efficacy, safety and tolerability of sibutramine hydrochloride (1, 5, 10, 15, 20 and 30mg daily) in obese patients for up to 24 weeks. • Bray GA, et al. Sibutramine produces dose-related weight loss. • Bray GA, et al. A double-blind randomized placebo-controlled trial of sibutramine.	 Obesity Research 1999; 7:189-98. Obesity Research 1996; 4:263-70.
BPI 858	Trial BPI 858: A double-blind, placebo-controlled study to evaluate the acute and chronic effects of sibutramine 10 and 30mg on resting metabolic rate in healthy obese women. Seagle HM, et al. Effects of sibutramine on resting metabolic rate and weight loss in overweight women.	 Obesity Research 1998; 6:115-21.
Cuellar (2000)	Six-month treatment of obesity with sibutramine 15mg; A double-blind, placebo-controlled monocenter clinical trial in a Hispanic population.	Obesity Research 2000; 8:71-82.
Fanghanel (2000)	• A clinical trial of the use of sibutramine for the treatment of patients suffering essential obesity. • Second phase of a double-blind study clinical trial on sibutramine for the treatment of patients suffering essential obesity: 6 months after treatment cross-over.	International Journal of Obesity 2000; 24:144-50 International Journal of Obesity 2001; 25:741-7.
Fanghanel (2003)	Safety and efficacy of sibutramine in overweight Hispanic patients with hypertension.	Advances in Therapy 2003; 20:101-13.
Faria (2002, 2005)	• Effects of sibutramine on abdominal fat mass, insulin resistance and blood pressure in obese hypertensive patients. • Effects of sibutramine on the treatment of obesity in patients with arterial hypertension.	Diabetes, Obesity and Metabolism 2005; 7(3):246-53. Arquivos Brasileiros de Cardiologia 2002; 78:172-80.
Hainer (2001)	• Abstract: Czech trial of sibutramine in the treatment of obesity: multicentre randomized study. • Sub-group: Psychobehavioral and nutritional predictors of weight loss in obese women treated with sibutramine.	International Journal of Obesity and Related Metabolic Disorders 2001; 25(Suppl 2):S107. International Journal of Obesity & Related Metabolic Disorders 2005; 29(2):208-16.

Trial/First author	Protocol/Publication title	Publication citation
Halpern (2002)	Evaluation of efficacy, reliability, and tolerability of sibutramine in obese patients, with an echocardiographic study.	Revista do Hospital das Clinicas 2002; 57:98–102.
Hauner (2004)	• Weight reduction by sibutramine in obese subjects in primary care medicine: The SAT study. • Sub-group analysis: Prediction of successful weight reduction under sibutramine therapy through genotyping of the G-protein β_3 subunit gene (GNB3) C825T polymorphism.	Experimental and Clinical Endocrinology and Diabetes 2004; 112:201-7. Pharmacogenetics 2003; 13:453-9
Hwu (2003)/ Hung (2005)	• Abstract: Hwu C-M, et al. Sibutramine treatment enhances weight loss and reduces waist circumference in obese Chinese type 2 diabetic patients. • 1 centre analysis: Hung Y-J, et al. Sibutramine improves insulin sensitivity without alteration of serum adiponectin in obese subjects with type 2 diabetes.	Journal of Parenteral and Enteral Nutrition 2003; 27:S12-S13. Diabetic Medicine 2005; 22(8):1024-30.
Kaya (2004)/ Aydin (2004)	• Kaya A, et al. Efficacy of sibutramine, orlistat and combination therapy on short-term weight management in obese patients. • Aydin N, et al. Orlistat, sibutramine, or combination therapy: Which performs better on waist circumference in relation with body mass index in obese patients?	Biomedicine and Pharmacotherapy 2004; 58:582-7. Tohoku Journal of Experimental Medicine 2004; 202:173-80.
Kim (2001)	Abstract: Efficacy of sibutramine in preobese and obese class I	International Journal of Obesity 2001; 25(Suppl 2):S117.
Milano (2005)	Use of sibutramine, an inhibitor of the reuptake of serotonin and noradrenaline, in the treatment of binge eating disorder: A placebo-controlled study.	Advances in Therapy 2005; 22(1):25-31.
Porter (2004) *	The Long-term Outcomes of Sibutramine Effectiveness on Weight (LOSE Weight) study: Evaluating the role of drug therapy within a weight management program in a group-model health maintenance organization.	American Journal of Managed Care 2004; 10:369-76.
Redmon (2003)	One-year outcome of a combination of weight loss therapies for subjects with type 2 diabetes: A randomized trial.	Diabetes Care 2003; 26:2505-11.
Sanchez-Reyes (2004)	Use of sibutramine in overweight adult Hispanic patients with type 2 diabetes mellitus: A 12-month, randomized, double-blind, placebo-controlled clinical trial.	Clinical Therapeutics 2004; 26:1427-35.
SB 104	Trial SB 104: Multicentre, randomised, double-blind, placebo-controlled study to assess the effects of sibutramine on left ventricular mass in obese patients during weight reduction. • Zannad F, et al. Effects of sibutramine on ventricular dimensions and heart valves in obese patients during weight reduction.	American Heart Journal 2002; 144:508-15.
SB 1043	Trial SB 1043: A double-blind, placebo-controlled, dose-ranging study to evaluate the weight reducing activity of sibutramine hydrochloride in obese patients. • Hanotin C, et al. Efficacy and tolerability of sibutramine in obese patients: A dose-ranging study.	International Journal of Obesity and Related Metabolic Disorders 1998 22:32-8.
SB 1047	Trial SB 1047: Long-term treatment of mild to moderate obese patients with sibutramine. • Smith IG, et al. Randomized placebo-controlled trial of long-term treatment with sibutramine in mild to moderate obesity. .	Journal of Family Practice 2001; 50:505-12
SB 2057	Trial SB 2057: A double-blind, placebo-controlled study to evaluate the weight reducing and anorectic activity of sibutramine in obese hypertensive subjects and to determine the anti-hypertensive effects of weight reduction. • Hazenberg BP. Randomized, double-blind, placebo-controlled, multicenter study of sibutramine in obese hypertensive patients. .	Cardiology 2000; 94:152-8
SB 3051	Trial SB 3051: Sibutramine versus placebo in obese patients with stage II diabetes. • Finer N, et al. Sibutramine is effective for weight loss and diabetic control in obesity with type 2 diabetes: a randomised, double-blind, placebo-controlled study.	Diabetes, Obesity & Metabolism 2000; 2:105-12.
SB 5075	Trial SB 5075: A randomised, double-blind, placebo-controlled, parallel group, multicentre trial with sibutramine in the	

Trial/First author	Protocol/Publication title	Publication citation
	treatment of obese type II diabetic patients receiving sulphonylureas. • Serrano-Rios M, et al. Role of sibutramine in the treatment of obese type 2 diabetic patients receiving sulphonylurea therapy. .	Diabetic Medicine 2002; 19:119-24
SB 5078	Trial SB 5078: A multicentre, double-blind, placebo-controlled trial, followed by an open treatment phase, to evaluate the effects of treatment with sibutramine upon obese Type II diabetic subjects currently untreated with antidiabetic medication. • Kaukua JK, et al. Health-related quality of life in a randomised placebo-controlled trial of sibutramine in obese patients with type II diabetes. • Subgroup analysis: Bach DS, et al. Absence of cardiac valve dysfunction in obese patients treated with sibutramine.	International Journal of Obesity and Related Metabolic Disorders 2004; 28:600-5. Obesity Research 1999; 7:363-9.
SB 5084	Trial SB 5084: A single centre, double-blind, placebo-controlled trial to evaluate the effect of treatment with sibutramine on energy expenditure in healthy obese subjects. • Hansen DL, et al. The effect of sibutramine on energy expenditure and appetite during chronic treatment without dietary restriction.	International Journal of Obesity and Related Metabolic Disorders 1999; 23:1016-24.
SB 6085	Trial SB 6085: A randomised, double-blind, placebo-controlled, parallel group, multicentre trial with sibutramine in the treatment of obese Type II diabetic patients receiving metformin. • McNulty SJ, et al. Multicenter Sibutramine Study Group. A randomized trial of sibutramine in the management of obese type 2 diabetic patients treated with metformin.	Diabetes Care 2003; 26:125-31.
SB 6087	Trial SB 6087: A study of the effects of sibutramine on the insulin sensitivity of obese patients with non-insulin dependent diabetes mellitus. • Abstract: Peirce NS, et al. The effect of sibutramine on weight loss and glucose metabolism in obese patients with type 2 diabetes mellitus. .	British Journal of Clinical Pharmacology 1999; 48:880P
SB 6090	Trial SB 6090: A double-blind, parallel-group, placebo-controlled study of the safety and efficacy of sibutramine in the treatment of obese patients. • Abstract: Gonzalez-Barranco J, et al Sibutramine reduces the carbohydrate craving in obese patients.	International Journal of Obesity and Related Metabolic Disorders 2000; 24(Suppl 1):S177.
Tambascia (2003)	Sibutramine enhances insulin sensitivity ameliorating metabolic parameters in a double-blind, randomized, placebo-controlled trial.	Diabetes, Obesity and Metabolism 2003; 5:338-44
Tankova (2003, 2004)	• Sibutramine in the treatment of obesity in type 2 diabetic patients and in nondiabetic subjects. • Subgroup analysis: Sibutramine in the treatment of obesity in type 2 diabetic patients.	Acta Diabetologica 2004; 41:146-53. Endocrinologia 2003; 8:257-65
Wadden (2005)	Randomized trial of lifestyle modification and pharmacotherapy for obesity.	New England Journal of Medicine 2005; 353:2111-20.
Walsh (1999)	The effect of sibutramine on resting energy expenditure and adrenaline-induced thermogenesis in obese females.	International Journal of Obesity 1999; 23:1009-15.
Supportive trials		
KD 9618	Trial KD 9618: Multicentre, double-blind, placebo-controlled, randomised parallel-group comparison to show the equivalence of weight reduction of continuous therapy with sibutramine 15mg and an interval therapy over 48 weeks in obese patients. • Wirth A, et al. Long-term weight loss with sibutramine: a randomized controlled trial.	JAMA 2001; 286:1331-9.
SB 1048	Trial SB 1048: A randomised, placebo-controlled, double-blind, parallel group, multicentre trial of the effects on maintenance of	

Trial/First author	Protocol/Publication title	Publication citation
	weight loss, of treatment with sibutramine in combination with a recommended diet and exercise programme. • Hansen D, et al Predictors of weight loss and maintenance during 2 years of treatment by sibutramine in obesity. Results from the European multi-centre STORM trial. • James WP et al. Effect of sibutramine on weight maintenance after weight loss: a randomised trial. STORM Study Group. • Rossner S. Sibutramine: Antidepressive agent tested against obesity. • Toubro S, et al. The effect of sibutramine for the maintenance of weight loss. A randomized controlled clinical trial. • van Baak MA, et al. Leisure-time activity is an important determinant of long-term weight maintenance after weight loss in the Sibutramine Trial on Obesity Reduction and Maintenance (STORM trial). • Abstract: Astrup A, , et al. Initial weight loss response to sibutramine predicts 2 years outcome in STORM.	International Journal of Obesity and Related Metabolic Disorders 2001; 25:496-501. Lancet 2000; 356: 2119-25. Lakartidnengen 2001; 98:1802-3 Ugeskrift for Laeger 2001; 163:2935-40. American Journal of Clinical Nutrition 2003; 78:209-14 International Journal of Obesity and Related Metabolic Disorders 2001; 25(Suppl 2):S104
SB 1049	Trial SB 1049: Efficacy and tolerability of sibutramine versus placebo in maintenance or improvement of weight loss, in obese patients, following a very low calorie diet. • Apfelbaum M, et al. Long-term maintenance of weight loss after a very-low-calorie diet: a randomized blinded trial of the efficacy and tolerability of sibutramine.	American Journal of Medicine 1999; 106:179-84.

* Data from this trial are presented as key and supportive evidence.

The submission presented meta-analyses of 40 of the head-to-head randomised trials. Two trials (Ballard, et al 2001; and Hainer et al, 2001) contained inadequate data to be included in the meta-analyses.

8. Results of Trials

In the three analyses presented, a trial based meta analysis, a patient level analysis of all patients and analysis of patients eligible under the requested patient level PBS restriction, the proportion of patients achieving a $\geq$ 5% weight loss was consistently higher in the sibutramine plus lifestyle modification group (approximately 50%) than in the lifestyle modification alone group (approximately 20%).

Other weight-loss outcomes presented in the submission were changes from baseline in BMI and weight.

Treatment with sibutramine was associated with significant increases in systolic and diastolic blood pressure and increases in pulse rate. Sibutramine was also associated with higher rates of headache, constipation, and dry mouth compared with placebo.

9. Clinical Claim

The submission claimed that sibutramine has significant clinical advantages over standard medical management, but has more toxicity. The PBAC had doubts about the extent of clinical benefit claimed in the submission.

10. Economic Analysis

A preliminary trial-based economic evaluation was presented. The choice of the cost-effectiveness approach was considered valid. The resources included were drug costs over six months.

The trial-based incremental cost/extra patient achieving a ≥ 5% reduction in body weight was < $15,000.

A modelled economic evaluation was presented. The choice of the cost-utility approach was considered valid. The resources included were drug costs, and the costs associated with cardiovascular events and stroke, type 2 diabetes and diabetes-related complications.

The base case modelled incremental discounted cost per extra discounted quality adjusted life year (QALY) gained was between $15,000 - $45,000. The model was sensitive to assumptions regarding long-term weight loss and the duration of the model, about which there is considerable uncertainty.

The PBAC noted that there were a number of issues with the modelled economic analysis.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the cost to Government would be around $30 to 60 million by year 3. The PBAC was concerned about the cost of listing sibutramine due to usage uncertainty and considered the net financial cost was underestimated.

12. Recommendation and Reasons

The PBAC noted that the restriction proposed by the submission appropriately attempted to target a population at high risk of cardiovascular disease. An outstanding matter with the restriction was how often people would be eligible for re-treatment with sibutramine. The modelled economic evaluation assumed that patients who do not respond after 6 months of therapy received no further treatment and were not allowed any further attempts at weight loss with sibutramine. However, the restriction did not limit therapy to any specific duration.

The PBAC was concerned about total cost to the PBS of listing sibutramine and the large potential for use outside of the restriction. The PBAC agreed that the submission's estimate of a net financial cost to the PBS of $30-$60 million in Year 3 of listing was likely to be an underestimate. Potential for use beyond the restriction exists in: patients with a BMI < 35 kg/m^2 (especially as according to the WHO classification a person with BMI of > 30 is considered obese); patients without two of the specified risk factors; and patients who have not tried diet and exercise and patients over 65 years of age.

The PBAC did not accept that placebo for standard medical management (consisting of lifestyle modification; ie a reduced calorie diet and/or exercise) was the only appropriate comparator. Surgical interventions such as gastric banding are also an appropriate comparator. The Committee noted that this procedure is one of the most rapidly expanding surgical procedures at the present time, and although not yet a standard practice for treating obesity, it is rapidly becoming so.

The Committee considered that the clinical trial evidence that sibutramine plus lifestyle modification is more effective at producing a ≥ 5% weight loss than life style modification alone is reasonable, but remained unconvinced that this is a sufficient weight loss in the very

obese patient group targeted by the restriction, especially in the absence of evidence that this benefit is sustained in the long term. The Committee also questioned how the benefit of sibutramine treatment would compare against other treatments such as gastric banding. Furthermore, the PBAC considered 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 submission did not provide an analysis of the proportion of patients achieving different levels of weight loss above the 5% or 10% levels. The weight-loss distribution would be more informative than the meta-analysis which shows that the mean weight loss, after 6 months of therapy, for an average size person with a BMI of 35 (approximately 105 kg) is 3.8kg. Other issues were the long term safety of sibutramine, and that any positive results of therapy are conditional upon having successful lifestyle modification at the same time as taking the drug.

The PBAC noted that there were a number of issues with the modelled economic analysis, which extrapolated the surrogate outcomes in the trials to final endpoints, in particular, the implausibly high diabetes mortality by use of the UKPDS risk engine, which overestimates the Australian mortality rates by 2-3 times. The Committee accepted that the model appropriately did not omit the direct effects of sibutramine in increasing blood pressure.

Overall, the model was considered to overestimate the potential benefits that are likely to accrue from the drug therapy. The incremental cost per Quality Adjusted Life Year (QALY) was considered to be high when compared to other lifestyle modifications, although it was noted that the intended population is at high risk of adverse events.

The PBAC rejected the submission because of doubts about the extent of clinical benefit, the resulting uncertain cost-effectiveness and a high potential for use outside the restriction.

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 has sought listing in a patient population at high risk of cardiovascular disease and diabetes and this was acknowledged by the PBAC. The sponsor believes that drug treatment for severe obesity is an effective part of a holistic approach that also includes diet and life style modification and that there is a clinical role for the use of sibutramine to treat severe obesity prior to surgical intervention. The sponsor is working to understand and resolve the issues outlined by the PBAC in order to demonstrate that sibutramine is a cost-effective treatment in patients with severe obesity.