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Submission No. 74
(Inq into Obesity)
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2 June 2008

Committee Secretary
Standing Committee on Health and Ageing
House of Representatives
PO Box 6021
Parliament House
CANBERRA ACT 2600.

Email: haa.reps@aph.gov.au

Dear Committee Secretary

Review of Obesity in Australia
Submission by Merck Sharp & Dohme (Australia) Pty Ltd

Merck Sharp & Dohme (Australia) Pty Ltd welcomes the opportunity to provide input to the Expert Panel as part of the review of the Review of Obesity in Australia.

The Australian subsidiary of Merck & Co., Merck Sharp & Dohme (Australia) Pty Ltd has grown to become one of Australia's largest pharmaceutical companies as well as one of the country's most significant research and development investors. Our investments support Australian R&D from clinical trials to research fellowships and untied grants. Currently, the company is involved in 32 Phase I-IV clinical trials, in more than 100 sites across Australia. These trials are investigating an array of therapeutic areas; in particular, cardiovascular disease, diabetes, osteoporosis, cancer and obesity.

Merck Sharp & Dohme (Australia) Pty Ltd is also expanding into the therapeutic area of obesity. The company has developed a weight loss enhancing drug, which is in the late stage (Phase III) of development. Clinical trials are currently being undertaken to investigate the medicine's effects of weight loss and prevention of weight gain in patients who are obese or overweight and have other co-morbidities. Merck Sharp & Dohme (Australia) is happy for its submission to be made public.

If you have any inquiries regarding our submission, please contact me using the details provided below.

Yours sincerely
Merck Sharp & Dohme (Australia) Pty Limited

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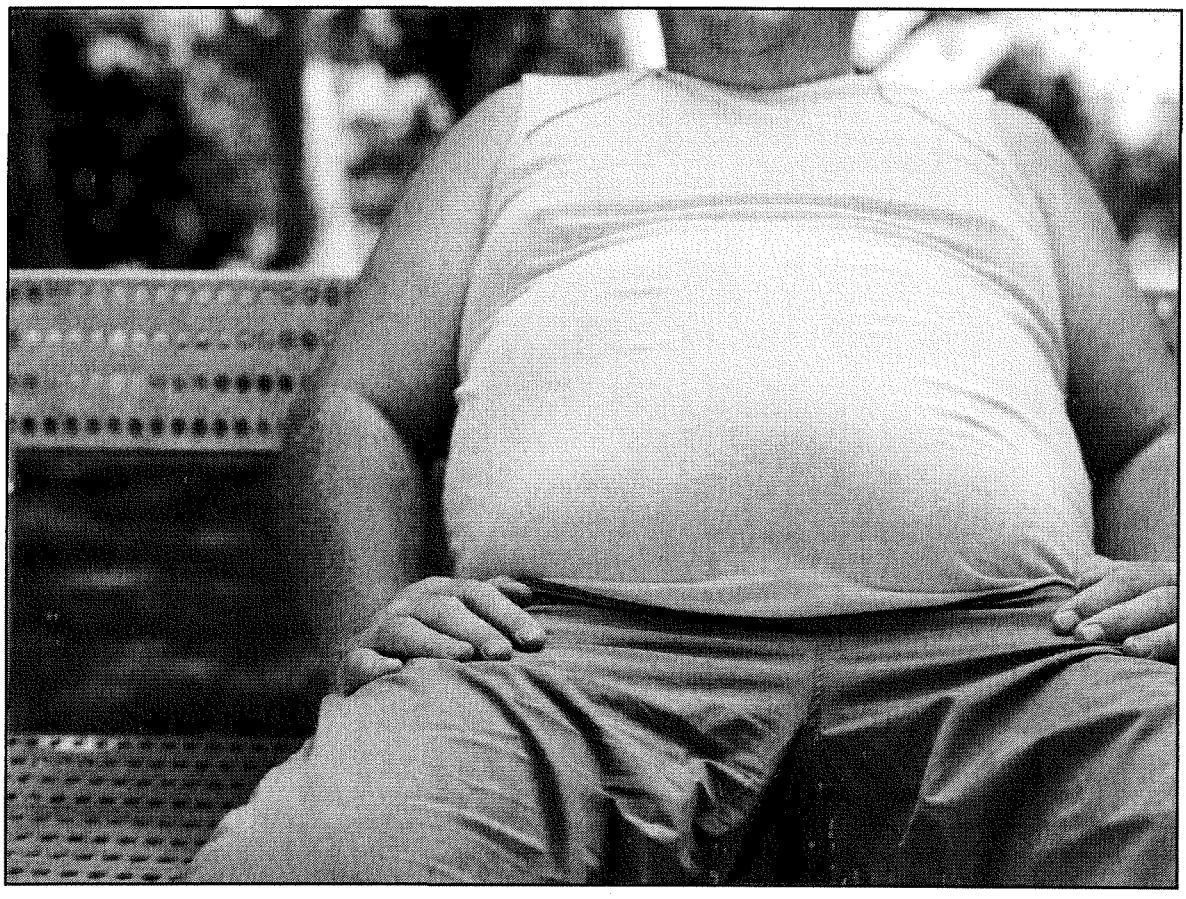
MERCK SHARP & DOHME
Finding better ways

Review of Obesity in Australia Submission



by
Merck Sharp & Dohme (Australia) Pty Ltd

June 2008

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GLOSSARY

Morbidity	The state of being diseased, sick or unhealthy
Pharmacotherapy	Treatment with medicine
Prevalence	The total number of cases of the disease in the population at a given point in time

EXECUTIVE SUMMARY

Obesity is one of the main risk factors in the overall burden of death and disease.

The disease has been linked to an increased risk of developing morbidities including: cardiovascular disease, type 2 diabetes, hypertension, dyslipidaemia, cerebrovascular disease, sleep apnoea and osteoarthritis. The development of these morbidities also increases the risk of death.

Australia, comparable to other developed countries, is also in the midst of an obesity epidemic. Australian adults, of all ages, are about 6-7 kg heavier than their same-age counterparts were 20 years ago and the majority (59%) of Australian adults now carry excess body fat: 33% are overweight and 26% are obese.

This epidemic is occurring despite the availability of clear recommendations on the role of diet and lifestyle to manage body weight, and the ready accessibility of weight loss educational resources. Adherence among Australians to lifestyle interventions to lose weight is low and their success in maintaining a long-term healthy weight is modest.

A need exists within Australia for the use of Weight loss pharmacotherapy in the treatment of obesity, and the NHMRC Guidelines endorse pharmacotherapy as an appropriate weight loss intervention in these individuals.

In Australia, only two pharmacotherapies are approved for the long-term treatment of obesity, however, neither of these are Pharmaceutical Benefits Scheme (PBS) listed so patient access is limited to those who can afford to pay for treatment.

Merck Sharp & Dohme (Australia) proposes that:

- The integration of weight loss pharmacotherapy into current management of obesity would be of benefit to the overall management of weight loss.
- Listing of weight loss medications on the PBS for appropriate patients is the best way to secure this integration.
- All weight loss medications should be given in conjunction with a reduced calorie diet and integrated into the overall management plan.
- Adjunct support programs for health professionals provided by the manufacturers of the weight loss medicines may be appropriate.

INTRODUCTION

The prevalence of obesity is increasing throughout both developed and undeveloped countries. Disturbingly, the disease is now recognised as a significant threat to human health, being one of the main risk factors in the overall burden of death and disease.

Obesity increases the risk of developing many chronic diseases, including Type 2 diabetes, cardiovascular disease, osteoarthritis, sleep apnoea and some cancers (NHPA website xxx). In the US, the disease is replacing smoking as the most significant contributor to preventable illness and premature death (Haslam 2005).

Australia's situation is comparable to other developed countries in that it is also in the midst of an obesity epidemic, which is placing a great burden on the nation's individuals, communities and the broader society. For example, the economic, social and psychological costs of the disease are considerable. In 2005, the total financial cost of obesity in Australia was estimated at $3.767 billion. Of this, $873 million contributed to health system costs and $1.7 billion were the estimated productivity costs (Access Economics 2006).

More measures need to be undertaken in Australia to offset the burden of obesity because despite the ready availability of access to weight loss education and resources, the prevalence of the disease is continuing to grow.

Merck Sharp & Dohme (Australia) (MSDA) believes multiple level actions in the management of the disease are required, for example at the levels of the individual, the community and the political arena. The company also believes the emerging technology of weight loss pharmacotherapy has a valid role in the management of obesity.

In accordance with the business focus of our company, the scope of this submission is contained to the medical management of obese individuals. In this context, the submission discusses:

- the measurement of excess weight in individuals
- the prevalence of overweight and obese individuals in Australia
- the health impacts associated with being overweight and obese
- the role of pharmacotherapy in weight management.

BACKGROUND

Measuring obesity

Obesity is the accumulation of excess fat in the body.

The most commonly used method for measuring obesity of an individual is the Body Mass Index (BMI). While this method does not directly measure the amount of body fat, it is a more accurate measure than body weight alone and a reasonable method for estimating overall body fat for most people.

BMI is calculated as weight (in kilograms) divided by height (in metres) squared.

BMI = weight/height^2

The World Health Organisation (WHO) has classified thresholds of BMI for adults, based on evidence of increased risk of chronic disease and mortality (WHO 2000) (**Table 1** below). An adult with a BMI greater than or equal to 25 and lower than 30 is classified as overweight. One with a BMI greater than or equal to 30 is classified as obese and this is the internationally accepted standard definition of adult obesity.[1]

Australia has adopted the WHO thresholds as its national standards for measuring body fat. (NHDC 2003).

Table 1: WHO Classification of BMI thresholds

BMI (kg/m^2)	Classification
<18.5	Underweight
18.5 to <25	Healthy weight range*
25 to <30	Overweight
≥30	obese

* Healthy weight range for Asians was recently updated to BMI of 18.5 to <23 (Haslam 2005)

THE PREVALENCE OF OVERWEIGHT AND OBESITY IN AUSTRALIA

Alarmingly, Australian adults, of all ages, are about 6-7 kg heavier than their same-age counterparts were 20 years ago (AIHW 2004). Accordingly, the proportion of then who are overweight or obese has also increased. Currently, the majority (59%) of Australian adults carry excess body fat, with 33% being overweight and 26% being obese (SAND Abstract No 69 2004-5) (**Figure 1**).

[1] The WHO recognises some ethnic groups may be unsuitable for the application of these classifications.

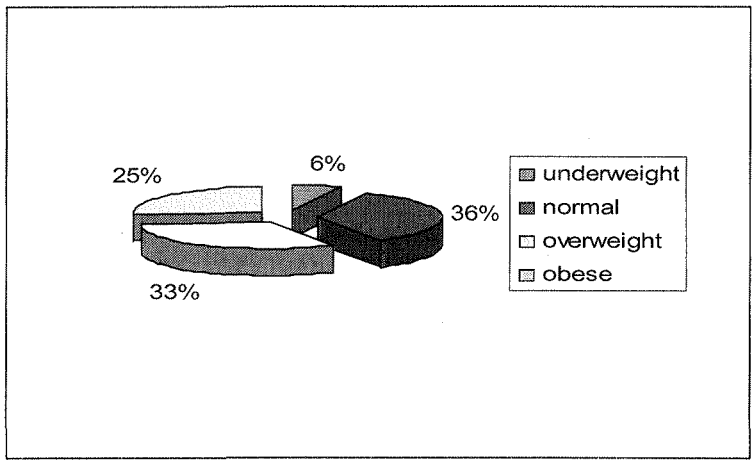

Figure 1: Prevalence of BMI thresholds in Australian adults

In 1990, 1995 and 2000, the Australian Bureau of Statistics undertook three National Health Surveys on behalf of the Australian Institute of Health and Welfare. The surveys' data was analysed by the NSW Centre for Overweight and Obesity to find out: (1) the national prevalence of overweight and obese individuals; (2) the effects ageing has on the prevalence of overweight and obese individuals; and (3) the relationship between birth cohorts and BMI (Allman-Farinelli 2006). The data analyses revealed that:

- Men and women of all ages (born since 1925) were heavier in 2000 than in 1995 or 1990.
- A greater proportion of people of all ages were overweight in 2000 than in earlier years.
- A greater proportion of people of all ages were obese in 2000 than in earlier years.
- Weight increases with age in almost all birth cohorts.
    - Men born between 1966-1970 show the most dramatic increases in average BMI over the previous 10 years. At the current rate of increase, the average male in this group is expected to have a BMI by 2010 that almost puts him in the obese range (forecast BMI 28.7 kg/m^2).
    - Women born between 1951 to 1955 have been predicted to be the most overweight group by 2010 (forecast average BMI 28.4 kg/m^2).

Self-identification of being overweight or obese

Interestingly, the majority (89.3%) of obese Australians can correctly identify themselves as being overweight. However, this identification is less likely to be correct for overweight individuals, as 40% of them do not recognise they carry excess weight (SAND Abstract No 69 2004-5).

The diminished ability of individuals to correctly identify they are overweight may be a result of the high prevalence of overweight Australians. Their ubiquity may be altering general perceptions of what an average weight for height should be so that overweight or obese individuals are being incorrectly perceived as being of "normal" weight.

Some examples of height and weight combinations that would be classified as overweight or obese are provided in **Table 2** below.

Table 2: Examples of heights and weights resulting in BMI classifications of overweight or obese

Height	Weight range for overweight classification	Weight range for obese classification
180cm (6ft)	87-97kg	≥98kg
173cm (5ft 9 inches)	75-89kg	≥90kg
165cm (5ft 6 inches)	68-81kg	≥82kg
155cm (5ft 2 inches)	62-71kg	≥72kg

THE HEALTH IMPACTS ASSOCIATED WITH BEING OVERWEIGHT AND OBESE

"Corpulence is not only a disease itself, but the harbinger of others". **Hippocrates**

The accumulation of excess fat in the body is associated with a number of health risks. As such, obesity should be viewed as a chronic disease rather than a cosmetic or body-image issue.

Excess weight and morbidity

Excess body weight has been linked with an increased risk of developing several other morbidities including: cardiovascular disease, type 2 diabetes, hypertension, dyslipidaemia, cerebrovascular disease, polycystic ovarian syndrome, osteoarthritis, gout and neural tube defects (Table 3).

Studies of overweight or obese patients show that the incidence of co-morbidities in overweight and obese are significant. For example, approximately one third of this group have hypertension, around 16% have elevated cholesterol, 9% have type 2 diabetes and 9% have coronary or peripheral vascular disease (SAND Abstract No. 71 2004-5).

Some of these morbidities—for example, type 2 diabetes and dyslipidaemia—result from the metabolic consequences of obesity. Other diseases—such as osteoarthritis, sleep apnoea and asthma—are directly linked to excess body weight.

An association also exists between the location on the body of excess fat deposition and weight-related co-morbidities. For example, excess fat in the abdomen, that is out of proportion to total body fat, is an independent predictor of type 2 diabetes, dyslipidaemia, hypertension and cardiovascular disease (Curioni and Andre' 2008).

Even a modest weight gain has a deleterious effect upon health because the risk of these co-morbidities developing increases from a BMI of about 21.0 kg/m^2.

Table 3: Morbidity in obesity (Jung 1997, Mathers et al 1999, Swinburne et al 2004, Kopelman 2007)

Cardiovascular	Hypertension	**Uterus**	Endometrial cancer
	Coronary heart disease		Cervical cancer
	Cerebrovascular disease e.g. ischemic stroke	**Urological**	Prostrate cancer
	Varicose veins		Stress incontinence
	Deep vein Thrombosis		Kidney cancer
	Hypertension	**Skin**	Sweat rashes
Respiratory	Breathless		Fungal infections
	Sleep apnoea		Lymphoedema
	Hypoventilation Syndrome		Cellulitis
	Pulmonary hypertension		Acanthosis nigricans
Gastrointestinal	Hiatus hernia	**Liver**	Non-alcoholic fatty liver disease
	Cancer: colorectal		Non-alcoholic steatohepatitis
Metabolic	Dyslipidaemia	**Orthopedic**	Osteoarthritis
	Insulin resistance		Gout
	Diabetes mellitus	**Endocrine**	Growth hormone and IGF1 reduced
	Polycystic ovarian syndrome		Reduced prolactin response
	Hyperandrogenisation		Hyperdynamic ACTH response to CRH
	Menstrual irregularities		Increased urinary free cortisol
	Metabolic Syndrome		Altered sex hormones
Neurology	Nerve entrapment		
	Proteinurea	**Pregnancy**	Obstetric complications
Breast	Breast cancer		Caesarean operation
	Male gynaecomastia		Large babies
			Neural tube defects

Excess weight and mortality

Excess body weight, in addition to increasing the risk of developing co-morbidities, also increases the risk of death from the morbidities. Compared to people of normal weight the risk of death for people of excess weight is:

- 30% higher for overweight people with BMI of 25 to <27 kg/m^2
- 60% higher overweight people with BMI of 27 to <29.0 kg/m^2
- More than doubled for overweight/obese people with BMI of 29 to <31 kg/m^2.

The Framingham study, a longitudinal landmark study that has investigated the development and progression of heart disease and its risk factors, predicted that life expectancy was reduced by more than three years in overweight 40 year old non-smokers, and by approximately six to seven years in obese 40 year old non-smokers (NHMRC 2003).

Diseases commonly associated with excess weight-related death include coronary heart disease, diabetes mellitus and some types of cancer (Jung 1997, NHMRC 2003).

Similar to the relationship between excess weight and morbidities, a relatively small increase in body weight is also associated with an increased risk of death (WHO 1997). For example, studies show that even marginally overweight people—a BMI of 25 to 27 kg/m^2—have an increased risk of death because of their excess weight, this risk escalating for obese people with BMI greater than 30 kg/m^2 (Jung 1997).

The magnitude of the burden of obesity

The following list provides examples of the adverse impact that excess weight and obesity has on the health of individuals and helps highlight the magnitude of the disease:

- Approximately half of all deaths of obese women can be attributed directly to their obesity (Jung 1997).
- Overweight women are five times more likely to develop diabetes than women of normal weight (Colditz et al 1995).
- Obese women are 28 times more likely to develop diabetes than women of normal weight (Colditz et al 1995).
- Overweight women have twice the risk of coronary heart disease than women of normal weight (Willet et al 1995).
- Obese women have almost four times the risk of coronary heart disease than women of normal weight (Willet et al 1995).
- Obese women have twice the risk of pregnancies with neural tube defects than women of normal weight (Shaw et al 1996).
- Obese men and women are five times more likely to have hypertension that people of normal weight (Kopelman 2007).
- Obese 40 year olds have a life expectancy seven years shorter than people of normal weight (Peeters et al 2003).

AUSTRALIANS AND WEIGHT LOSS

Fundamentally, being overweight or obese is essentially a consequence of unbalanced energy intake and expenditure and lifestyle changes are fundamental to the management of being overweight or obese.

Evidence shows a reduction in total energy intake remains the basic mechanism whereby all dietary weight loss occurs (NHMRC 2003).

Education and lifestyle skills training are recommended by the National Health and Medical Research Council (NHMRC) Guidelines as the initial approach to treating overweight and obese individuals—including the provision of physical activity advice, dietary advice, support and regular monitoring of progress.

Despite clear recommendations on the role of diet and lifestyle to manage body weight, and the ready accessibility of educational resources in respect of this, Australians are finding it difficult to maintain a healthy weight—either with or without weight loss attempts.

Almost 50% of overweight adults and approximately 65% of the obese adults have made at least one attempt to lose weight in the previous 12 months (SAND abstract No 69 2004-5).

Of the overweight: 38.7% attempted to lose weight through diet and exercise; 11.3% through receiving GP advice; 4.9% through meal plans and; 4.7% through a weight loss program (**Figure 2**). Of the obese: over 50% reported trying diet and exercise; 20.1% had received GP advice; 10.4% had tried weight loss program; 9.2% had tried meal plans, and; 5.9% had tried prescribed medication (**Figure 2**).

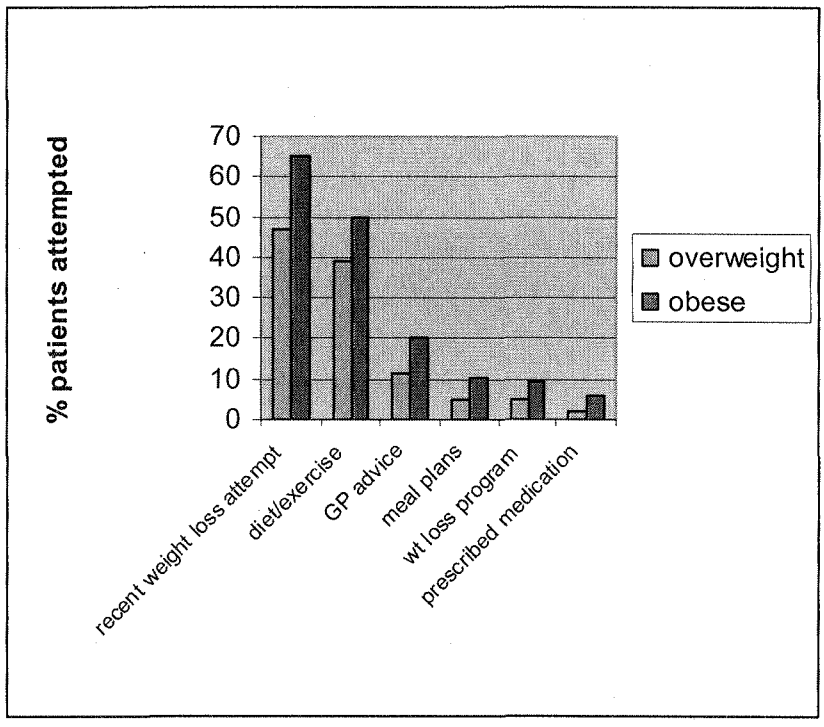

Figure 2: Methods of weight loss attempted by overweight or obese Australian adults

In the scientific literature, critical analyses of the long-term efficacy of diet and exercise also suggest that adherence to lifestyle interventions is low and that the long-term success of weight loss is modest (Scheen 2008). Additionally weight loss after diet is usually followed by gradual weight regain (Curioni 2008).

Therefore, at a societal level, diet and exercise and weight loss education have become insufficient methods for managing excess weight.

The current medical treatment strategies inadequately address the weight problems faced by Australian and more needs to be done to manage weight both at an individual, community, societal and policy level.

THE ROLE OF PHARMACOTHERAPY IN WEIGHT MANAGEMENT

The main promise of pharmacotherapy is its potential to improve longer term maintenance of weight loss by reducing hunger or increasing energy expenditure.

Weight loss medicines available in Australia

A number of medicines produce weight loss but many are not approved for that use (e.g. selective serotonin re-uptake inhibitors Prozac® and Lovan®) or they are recommended for short term use only (e.g. Dopaminergic agonists such as Duromine™ where a defined course of treatment should not exceeed three months duration).

In Australia, only two pharmacotherapies are approved for the long-term treatment of obesity: Sibutramine (Reductil®) manufactured by Abbott and Orlistat (Xenical®) manufactured by Roche.

Two other weight loss drugs are in the late stages of clinical development: Rimonabant, manufactured by Sanofi-Aventis and Taranabant, manufactured by Merck Sharp & Dohme. A brief description of these weight loss drugs is provided below.

Please note:

- All reported results represent the additional benefit of the medication, compared to the benefit of diet alone.
- While participating in the trials investigating the effects of these anti obesity medications all patients received a calorie-reduced diet.
- All weight loss medications should be given in conjunction with a reduced calorie diet.

Orlistat (Xenical®)

Orlistat produces weight loss by decreasing preventing ingested fats being absorbed by the body.

Clinical trials demonstrate that treatment with Orlistat is associated with weight loss, and significant improvement of risk factors, i.e. lowered LDL-cholesterol, reduced blood pressure, improved cardiovascular status, reductions in the number of diabetic patient. The weight loss was maintained while treatment continued and was evident even in patients where diet alone had failed to induce a significant weight loss.

As Orlistat decreases absorption of ingested fats, commonly observed mild side effects are fatty/oily stools, abdominal pain and flatulence.

Orlistat (Xenical®)

Effect on weight	Patients on average lost approximately 4kg more body weight An additional 21.4% of patients lost at least 10% of their body weight
Effect on risk factors	LDL cholesterol decreased by approximately 8% Systolic blood pressure decreased by approximately 1.5mmHg 14% more diabetic patients were able to reduce or stop taking their diabetes tablets The progression from a normal to a diabetic state was prevented or reversed Waist circumference decreased by almost 2cm
Source	*Xenical Product Information*

Sibutramine (Reductil®)

Sibutramine works by suppressing appetite and increasing resting metabolic rate.

Clinical trials demonstrate that treatment with Sibutramine is associated with significant weight loss, reductions in waist circumference, fat accumulation in the abdomen and fasting plasma glucose. Improvements in blood cholesterol have also been observed.

An observed side effect of Sibutramine was increased blood pressure, however, no clinically significant outcomes were associated with this.

Sibutramine (Reductil®)

Effect on weight	Almost 3 times as many patients maintained at least 80% of their original weight loss An additional 18% of patients lost at least 5% of their body weight
Effect on risk factors	Reduced waist circumference
Source	*Sibutramine Product Information*

Rimonabant

Rimonabant is a new type of medication currently being investigated for its effect on long term weight loss. The way in which this medication modulates human energy balance is not completely understood, however, studies suggest that weight loss induced by Rimonabant is due to both reducing food intake though regulation of appetite and increasing energy expenditure by altering the metabolic rate. Clinical trials demonstrate that treatment with

Rimonabant is associated with improvements in risk factors via reduced blood pressure, reduced waist circumference and improvements in cholesterol.

The effect of Rimonabant is mainly in the brain but it is possible the drug could effect a number of body systems unrelated to eating. Rimonabant is registered for use in Europe, where it is contraindicated for patients with severe depression/and/or those treated with antidepressive medications.

Rimonabant 20mg Daily

Effect on weight	Patients lost, on average, approximately 5kg more body weight
Effect on risk factors	HDL cholesterol increased by 3.5mg/dL Systolic blood pressure decreased by approximately 2 mmHg Waist circumference decreased almost 4cm
Source	*Curioni and Andre 2008. Cochrane Systematic Review*

Taranabant

Taranabant is a similar type of medication to rimonabant. The way in which this medication modulates human energy balance is not completely understood, however, studies suggest that weight loss induced by Taranabant is due to both reducing food intake though regulation of appetite and increasing energy expenditure by altering the metabolic rate. Clinical trials demonstrate that treatment with taranabant is associated with weight loss, a reduced numbers of patients with metabolic syndrome, reductions in waist circumference and blood pressure.

Taranabant 2mg Daily

Effect on weight	Patients on average lost approximately 5kg more body weight An additional 19.5% of patients lost at least 10% of their body weight
Effect on risk factors	LDL cholesterol decreased by 1.6% HDL cholesterol increased by 6.8% Systolic blood pressure decreased by 1.3mmHg The odds of a patients having metabolic syndrome was reduced by 40%. Waist circumference decreased almost 4cm
Source	*Gantz et al 2008.*

The integration of pharmacotherapy into current management

Merck Sharp & Dohme (Australia) proposes that pharmacotherapy should be integrated into the current management of obesity and that these medicines should be available to the public on the PBS to ensure this integration is successful.

Recent Australian surveys have revealed a need exists for the use of pharmacotherapy in the treatment of obesity. The surveys' results showed that almost 6% of obese adults have used medication as a method of weight loss (SAND abstract No 69 2004-5).

Furthermore, the NHMRC Guidelines endorse pharmacotherapy as an appropriate intervention for patients, recommending it be used as part of a comprehensive weight-loss program upon the meeting of two basic criteria:

- a BMI>30 kg/m2 (obese patients) or a BMI>27 kg/m2 with co-morbidities (overweight patients)
- failure to lose weight on a program of diet, exercise and behaviour therapy.

Yet no weight loss medicines are PBS listed so access to them is limited to patients who can afford to pay for treatment.

All PBS listed medicines have been evaluated by the Pharmaceutical Benefits Advisory Committee (PBAC) to ensure the drug is not only clinically effective but also cost-effective. Although guidelines recommend pharmacotherapy as clinically appropriate for obese patients and some overweight patients with co-morbidities, the appropriate patients within this group to receive subsidised medical treatment of obesity would be identified through the PBAC evaluation process (i.e. PBS eligible groups may be more restrictive than the groups that the NHMRC recommends should receive the medicines).

Successful management of obesity is likely to require multidisciplinary attention and a long term approach.

Considering that weight gain tends to increase with age, the listing of the weight loss medicines on the PBS would enable Australia's older members of society—those that need them most but can least afford them—to access the medicines.

Moreover, the ready availability of weight loss medicines through PBS listing would allow their easy integration into the overall management of the disease. The availability of these medicines for long-term use would also provide clinicians with another strategy to assist them in managing the disease, in addition to the emerging multidisciplinary team based approach for its management. Assisting with the latter already is the Medicare Benefits Scheme's extended consultations for care planning and case conferencing, which encourages patient referral to dieticians, exercise physiologists or specialist physicians (NHMRC 2003).

Pharmaceutical companies and medication support programs

As part of the listing of anti-obesity drugs on the PBS, it may be appropriate for the sponsoring companies to provide adjunct support programs to secure the quality use of these medicines. That is, support programs designed to help ensure the medicines are used by appropriate patient groups for treatment durations to achieve the desired health outcomes.

Pharmaceutical companies in Australia have a track record of providing successful support programs for other PBS reimbursed medicines in the framework of a Quality Use of Medicine (QUM) program. For example, when SINGULAIR (montelucast sodium) was first made available on the PBS for the treatment of asthma. Merck Sharp & Dohme (Australia), in conjunction with the National Asthma Council, conducted an education campaign for general practitioners.

Furthermore, pharmaceutical companies have extensive experience in providing educational, practice management and nursing support to Australian general practitioners to assist them in optimally managing complex disease areas. For example, Merck Sharp & Dohme (Australia) has successfully assisted GPs in managing chronic diseases such as osteoporosis and cardiovascular disease though the mdCare® chronic disease management program.

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