











## **THE PHARMACOLOGICAL MANAGEMENT OF OBESITY**

### **SUMMARY**

-  **The incidence and prevalence of obesity in Ireland is increasing.**
-  **Obesity is a risk factor for many diseases including cardiovascular disease, diabetes and arthritis.**
-  **Diet, exercise and lifestyle modifications are the mainstays of treatment of obesity.**
-  **Orlistat and sibutramine are licensed for the management of obesity.**
-  **Orlistat is a gastrointestinal lipase inhibitor and sibutramine is a centrally acting noradrenaline and serotonin re-uptake inhibitor.**
-  **Both agents have been shown to produce a significantly greater weight loss compared with placebo, however there is limited evidence on the long-term effects on morbidity and mortality.**
-  **The overall average weight reduction is modest (maximum 5kg over placebo at one year).**
-  **The choice of agent should be patient specific, based on contraindications, drug interactions, expected adverse effects and proposed duration of therapy.**

### **INTRODUCTION**

Obesity is a chronic condition characterised by an excess of body fat.<sup>1</sup> The World Health Organisation classifies obesity as having a body mass index (BMI - defined as the weight in kg divided by height in metres squared) of  $\geq 30 \text{ kg/m}^2$ . Overweight is classified as a BMI of  $25.0 - 29.9 \text{ kg/m}^2$ , and normal weight as a BMI of  $18.5 - 24.9 \text{ kg/m}^2$ .

Obesity is a multifactorial condition, with environmental factors, eating behaviour, stress, pre-existing medical conditions and genetic factors all contributing. Obesity should be considered as a disease state, rather than solely due to over indulgence.<sup>3</sup>

In Ireland, over the past 20 years, increasing affluence and changing lifestyles have altered the attitude to food.<sup>4</sup> 18% of the Irish population are obese (20% of men and 16% women) and 39% are overweight (46% of men and 33% of women). Since 1990, the prevalence of obesity has increased 1.25-fold in women, and 2.5-fold in men.<sup>2</sup>

There is a well-established relationship between excess body weight and such medical conditions as type 2 diabetes, cardiovascular disease, hypertension, dyslipidaemia, sleep apnoea, gallbladder disease, osteoarthritis and certain cancers.<sup>1,2,5,6</sup> Recently cases of type 2 diabetes have been identified in Caucasian adolescents.<sup>7</sup> This phenomenon is likely to become an issue in this country, and will have a major long-term impact on healthcare.

A modest weight reduction (10%) has many health benefits, including positive effects on mortality, hypertension, diabetes and dyslipidaemia.<sup>8</sup>

# MANAGEMENT

Identifiable risk factors for adult obesity are being overweight as a child, and having an obese parent. Prevention of obesity is critical, and childhood is potentially an ideal time. A combination of healthy eating and exercise are preventative measures to address developing weight problems.<sup>4</sup>

Efforts to prevent further weight gain in adults at risk of being overweight or obese are essential. For those whose health is at risk because of their obesity, and who are motivated to make lifestyle changes, a recommendation for weight loss is appropriate.<sup>6</sup> Lifestyle modifications such as altered diet, decreased calorific intake and increased exercise are the mainstays of treatments for obesity. Unless weight loss is sustained, any health improvements will not be maintained.

Maintenance of lifestyle changes is difficult for some patients, and some will regain any weight lost. There are now two therapeutic agents licensed for the treatment of obesity.

## ORLISTAT (XENICAL®)

**Overview:** Orlistat is a lipase inhibitor that produces weight loss by reducing the amount of dietary fat being absorbed. This leads to an increased excretion of fat in the faeces. Orlistat is licensed for use in conjunction with a mildly hypocaloric diet for the treatment of obese patients (BMI  $\geq 30\text{kg/m}^2$ ), or overweight patients (BMI  $\geq 28\text{kg/m}^2$ ) with associated risk factors. Treatment is indicated only in those patients who have lost at least 2.5kg over a period of 4 consecutive weeks on diet alone.<sup>9</sup>

**Trials:** A systematic review and subsequent randomised controlled trials (RCTs) have found that orlistat combined with a low calorie diet modestly increases weight loss in adults with obesity, compared with placebo plus diet.<sup>1</sup> Mean weight loss from trials shows a reduction of some 2 - 5kg per year over the weight decline with placebo.<sup>10</sup> A study looking specifically at the effect of orlistat on obese adults with coronary heart disease risk factors (type 2 diabetes, hypercholesterolaemia or hypertension) found that more orlistat-treated patients than placebo recipients maintained a weight loss of  $\geq 5\%$ . However, for a weight loss of  $\geq 10\%$ , there was no statistical difference between the placebo and treated groups.<sup>11</sup>

One review concluded that in patients with obesity, orlistat recipients were more likely to experience an improvement, and less likely to experience a deterioration, in glucose tolerance status than placebo recipients.<sup>12</sup>

In patients with obesity and type 2 diabetes, orlistat recipients had significantly greater reductions in glycosylated haemoglobin and fasting plasma glucose levels than placebo recipients.<sup>12</sup> The decrease in bodyweight with orlistat treatment is less in type 2 diabetic patients than in non-diabetic patients.<sup>9</sup>

The view that orlistat may be beneficial in patients with comorbid conditions related to obesity, such as diabetes and hyperlipidaemia is supported in several recent reviews.<sup>5,13</sup> One review noted that in some long-term studies, orlistat-treated patients had moderate decreases in diastolic blood pressure, insulin levels while fasting, and total cholesterol and LDL cholesterol, with a small cholesterol-lowering effect that was independent of weight loss.<sup>5</sup>

**Dose:** One 120mg capsule three times daily, to be taken immediately before, during or up to one hour after each meal.

**Duration of therapy:** Treatment should be discontinued after 12 weeks if the patient fails to lose at least 5% of their body weight. NICE guidance in the UK states that continuation of therapy beyond six months should be supported by evidence of a cumulative weight loss of at least 10% of body weight from the start of treatment.<sup>10</sup> Maximum duration of therapy is two years.<sup>9</sup>

**Side Effects:** The most common side effects are gastrointestinal, including oily spotting from the rectum (27%), flatus with discharge (24%), faecal urgency (22%), fatty/oily stool (20%), oily evacuation (12%), increased defecation (11%) and faecal incontinence (8%).<sup>9</sup> Severity appears to be related to dietary fat intake. The incidence of adverse effects decreases with prolonged use of orlistat.<sup>9</sup>

People taking orlistat may require vitamin supplements due to decreased absorption of fat-soluble vitamins.<sup>1,5,10,14</sup> If a multivitamin is recommended, it should be taken at least two hours after the administration of orlistat, or at bedtime.<sup>9</sup>

**Contraindications:** Orlistat is contraindicated in patients who have chronic malabsorption or cholestasis.<sup>5,9</sup>

**Interactions:** A reduction in cyclosporin levels has been observed when orlistat is co-administered, therefore it is recommended to monitor cyclosporin levels more frequently. Concomitant acarbose is not recommended. Other antidiabetic drug treatment may have to be closely monitored when taking orlistat because glucose tolerance improves with weight reduction. Patients on warfarin may also require close monitoring of the INR.<sup>1,5,9</sup>

## SIBUTRAMINE (REDUCTIL®)

**Overview:** Sibutramine is a centrally acting noradrenaline and serotonin re-uptake inhibitor, and has been shown to produce weight loss by enhancing satiety.<sup>15</sup>

It is licensed as adjunctive therapy within a weight management programme for obese patients with a BMI  $\geq 30\text{kg/m}^2$ , or overweight patients (BMI  $\geq 27\text{kg/m}^2$ ) with associated risk factors. It should only be prescribed, by a physician experienced in the treatment of obesity, to patients who have not responded to a weight-reducing regimen alone.<sup>15</sup>

**Trials:** Evidence from several RCTs showed sibutramine to be more effective than placebo at promoting modest weight loss in adults with a BMI of between 25 and  $40\text{kg/m}^2$ .<sup>1</sup> Mean weight loss was greater with sibutramine than with placebo, on average by between 4 and 5kg at 1 year.<sup>16</sup> The weight loss maximised after a few months, and was not sustained after stopping treatment.<sup>1,17-20</sup> Some of the studies were of two years' duration, although the licensed duration is one year, and patients maintained a weight loss for the entire study period.<sup>18,21</sup> One of the trials had a large number of drop-outs but included some patients who had doses of 20mg, which is above the licensed dose.<sup>21</sup> Some of the trials studied sibutramine-treated obese patients with type 2 diabetes, and weight loss was favourable over placebo.<sup>14,19</sup>

One RCT found that sibutramine caused modest weight loss in obese adults with controlled hypertension, but there was insufficient evidence on short-term safety, and no evidence on long-term safety.<sup>1,22</sup> Sibutramine-induced weight loss has been reported to result in improvements in serum levels of triglycerides, HDL cholesterol, uric acid and glucose, and in waist circumference and quality of life measures.<sup>5,22</sup> The clinical significance of these improvements has not been established.

**Dose:** The initial dose is 10mg once daily, increased if necessary to 15mg daily.<sup>15</sup>

**Duration of therapy:** Treatment should be discontinued after three months if weight loss is  $<5\%$  of initial bodyweight. Maximum duration of therapy is one year, since data over one year are limited.<sup>15</sup>

**Side Effects:** Common side effects are headache, hypertension, dry mouth, anorexia, constipation and insomnia. Mean increases in systolic and diastolic blood pressure (BP) and heart rate have been reported.<sup>1,14,15,17</sup>

In the first three months of treatment, BP and heart rate should be monitored every 2 weeks, and at regular intervals thereafter (Refer to SmPC Reductil®). Treatment should be discontinued if patients have an increase of 10bpm in heart rate or 10mmHg in systolic or diastolic BP at two consecutive visits. Treatment should also be discontinued in previously well-controlled hypertensives if BP exceeds 145/90mmHg on two consecutive readings.<sup>15</sup>

**Cautions:** According to the SmPC the use of sibutramine in patients with epilepsy is cautioned but no further details are given.<sup>15</sup>

**Contraindications:** Sibutramine is contraindicated in several patient groups, including those with a history of psychiatric illness, alcohol or drug abuse, congestive heart failure, transient ischaemic attacks, stroke or coronary artery disease; or patients with inadequately controlled hypertension, hyperthyroidism or benign prostatic hyperplasia with urinary retention.<sup>14,15</sup>

**Interactions:** Ketoconazole, itraconazole, erythromycin, clarithromycin and cyclosporin have the potential to increase sibutramine levels. Rifampicin, phenytoin, carbamazepine, phenobarbitone and dexamethasone may decrease sibutramine levels. Sibutramine inhibits serotonin reuptake, and because of the risk of serotonin syndrome (a condition caused by serotonin hyperstimulation which varies in severity from e.g. restlessness, diaphoresis to confusion and convulsions) it should not be used concomitantly with other drugs that also raise brain serotonin levels e.g. SSRIs, triptans or certain opioids. Caution is also advised with certain cough/cold remedies or decongestants since they may increase BP or heart rate. Two weeks should elapse between stopping sibutramine and starting monoamine oxidase inhibitors.<sup>15</sup>

**NOTE:** At the time of going to press, the Italian Ministry for Health has temporarily suspended sibutramine due to reports of serious cardiovascular adverse effects. The manufacturers of Reductil® have confirmed that 34 deaths have been reported to date in patients taking sibutramine.<sup>23</sup> Following on from this the Committee for Proprietary Medicinal Products, the scientific committee of the European Agency for the Evaluation of Medicinal Products, has initiated a review on the risk-benefit of sibutramine.<sup>24</sup>

## CONCLUSION

The treatment of obesity should focus on a combination of diet, exercise and behavioural modification. New therapeutic approaches to the treatment of obesity have been developed, which should be used alongside advice and support from appropriate healthcare professionals.

Orlistat works by reducing the amount of dietary fat absorbed and has few contraindications. Sibutramine works centrally by promoting a feeling of fullness. Sibutramine may only be prescribed to patients who have not adequately responded to an appropriate weight-reducing regimen alone, whereas orlistat should only be used if diet alone achieves a weight loss of greater than 2.5kg in the preceding four weeks. Risk-factor modification has been a secondary objective in most published studies. There are no published trials comparing sibutramine with orlistat. Both agents have been shown to produce a significant but modest reduction in weight compared with placebo, however there is limited evidence on the long-term effects on morbidity and mortality.

### Cost of 28 days Therapy (GMS March 2002)

Preparation	Cost
Orlistat (Xenical®) 120mg tds	€65.80
Sibutramine (Reductil®) 10mg od	€59.17
Sibutramine (Reductil®) 15mg od	€66.09

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