REVISED GUIDELINES FOR USE OF ANTI-OBESITY AGENTS:
ORLISTAT (XENICAL®) and SIBUTRAMINE (REDUCTIL®)

Produced by Tayside Medicines Information Centre, reviewed June 2008 by Dr M Murphy, University of Dundee and The Medicines Advisory Group

Orlistat (Xenical®) and sibutramine (Reductil®) are agents used for the management of obesity. Orlistat acts locally by blocking fat absorption from the gastro-intestinal tract. Sibutramine reduces appetite by modulating monoamine neurotransmitter activity in the CNS. Individually, these drugs may be tried in the management of obesity (combination therapy not recommended) but their use should be governed by strict criteria. The following guidelines are provided, and are based on NICE clinical guideline 43 – Obesity (December 2006), information from the manufacturer’s Summary of Product Characteristics for each drug and previous Tayside Drug & Therapeutics Committee recommendations.

WHICH PATIENTS?

Anti-obesity drugs MAY be considered for the following patients……

Obese patients with a BMI ≥ 30 kg/m², or BMI ≥ 27/28 kg/m² (sibutramine/orlistat respectively) with one or more weight-associated risk factors.

Such risk factors include:
- Cardiovascular disease i.e. angina, heart failure (sibutramine contra-indicated)
- Uncontrolled hypertension (sibutramine contra-indicated)
- Diabetes mellitus
- Sleep apnoea
- Hyperlipidaemia despite lipid-lowering therapy
- Severe respiratory problems including COPD or asthma
- Surgery: when weight loss is necessary in order for surgery to proceed.

For example:
- Hip replacement and other joint/orthopaedic operations
- Coronary artery bypass operations
- Aneurysm repair - abdominal and peripheral
- Significant abdominal herniation

… but ONLY after diet and lifestyle change has failed …

Anti-obesity drugs are only indicated for patients who cannot achieve or maintain an appropriate weight loss (suggested target 5-10% or more of body weight) over a course of dietetic surveillance (they should otherwise continue to receive diet and lifestyle advice and support). Drugs should never be used as the sole element of treatment. Thus patients should first be entered into a minimum 3 month structured weight management programme on the advice of a health care professional (may include a hospital or community dietician or practice nurse) trained in obesity management including the provision of diet and lifestyle advice and support. If some weight loss occurs but the target is not achieved, the opportunity should be given for a further 3 months attempt with diet alone. Orlistat’s license no longer requires a 2.5kg weight loss prior to prescription but adherence to a reduced fat diet before starting orlistat may assist in the reduction of unwanted GI side effects.
WHO SHOULD NOT BE TREATED?

- Orlistat (Xenical®) is contraindicated in breast-feeding, cholestasis and chronic malabsorption and is not recommended in pregnancy. There is no data to support its use in the elderly and it is not intended to be used in children. NICE guidance states that it should be used in those aged 18-75 only.

- Sibutramine (Reductil®) is contraindicated in those with psychiatric illness, major eating disorder, Tourette’s syndrome, history of drug or alcohol abuse, or on current (or use during prior 2 weeks) antidepressant, neuroleptic drug therapy, weight reduction drug therapy or tryptophan therapy. Avoid also in inadequately controlled hypertension (BP >145/90 mmHg), hyperthyroidism, severe hepatic or renal impairment, symptomatic BPH, phaeochromocytoma, narrow angle glaucoma, or if a history of coronary artery disease, congestive heart failure, arrhythmia, tachycardia, peripheral arterial occlusive disease or TIA or stroke. It is also contraindicated in pregnancy and breast-feeding and is unlicensed for those aged < 18 years or > 65 years. Women of childbearing potential should use an adequate method of contraception while taking sibutramine.

WHICH DRUG?

Each agent is unique in its site of action, either local in the GI tract (orlistat) or systemic in the CNS (sibutramine). Site of action may therefore have a bearing on the choice of drug since it influences their side effect profiles, potential interactions and precautions and contraindications. In any event, these agents should only be used within the terms of their individual product licenses. Combination therapy is not recommended.

Rimonabant (Acomplia® ▼) is a selective antagonist of cannabinoid type-1 (CB1) receptors. It is not recommended for use in NHS Scotland. For Scottish Medicines Consortium advice click here. Psychiatric adverse drug reactions, particularly depression have been identified as important safety issues with rimonabant. Click here for further information from the MHRA Drug Safety Update, May 2008.

DISCONTINUING TREATMENT

- Sibutramine is only licensed for continuous use up to 1 year. NICE recommends that orlistat treatment should not usually continue beyond 12 months, and never beyond 24 months. Evidence of efficacy and safety is limited beyond these periods.

- Treatment must be discontinued after 3 months in patients who have failed to lose 5% of their starting body weight. They are otherwise at risk of drug side effects in the absence of any therapeutic benefit.

- The value of continuing therapy is also in doubt if there is significant weight regain (e.g. 3-5 kg) on treatment after an initial weight loss.
ADVERSE EFFECTS and MONITORING

Orlistat (Xenical®)

Gastro-intestinal side effects are limited by dietary compliance (i.e. reduced fat intake) and it is therefore essential that these are discussed with the patient beforehand. They include abdominal pain/discomfort, flatus, oily discharge, faecal urgency and incontinence, oily stools and increased defecation. Other side effects include headache, respiratory infections, tooth and gingival disorders, fatigue, menstrual irregularity, anxiety, influenza, UTIs and hypoglycaemia.

Sibutramine (Reductil®)

These are relatively common and similar to the side effects seen on SSRI antidepressant therapy. They include anxiety, light-headedness, paraesthesia, sleep disturbance, increased sweating, dry mouth, altered taste, nausea, constipation (aggravated haemorrhoids), tachycardia, palpitations, generalised vasodilatation/flushing, and raised BP. Monitor blood pressure and pulse rate every two weeks for the first three months, then monthly for the next three months, then at least every 3 months thereafter. Discontinue treatment in patients who have an increase, at 2 consecutive visits, in resting heart rate of ≥10bpm or systolic/diastolic BP of ≥10mmHg. In previously well-controlled hypertensive patients, if blood pressure exceeds 145/90 mmHg at two consecutive readings, treatment should be discontinued.

DRUG INTERACTIONS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interacts with:</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>orlistat</td>
<td>fat soluble vitamins</td>
<td>↓absorption. Advise vitamin A, D &amp; E rich diet or give supplements</td>
</tr>
<tr>
<td></td>
<td>acarbose</td>
<td>Not established but avoid. Close monitoring of oral antidiabetic therapy advised</td>
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<tr>
<td></td>
<td>warfarin</td>
<td>Monitor INR (Long term use is associated with the possibility of ↓vitamin K absorption.)</td>
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<tr>
<td></td>
<td>ciclosporin</td>
<td>Possible ↓absorption of ciclosporin</td>
</tr>
<tr>
<td></td>
<td>amiodarone</td>
<td>Clinical relevance unknown. May ↓amiodarone plasma concentration (clinical &amp; ECG monitoring recommended).</td>
</tr>
<tr>
<td></td>
<td>oral contraceptives</td>
<td>No drug interaction. However additional contraceptive method recommended in case of oral contraceptive failure in severe diarrhoea.</td>
</tr>
<tr>
<td>sibutramine</td>
<td>ketoconazole, itraconazole, erythromycin, clarithromycin, ciclosporin &amp; other CYP3A4 inhibitors</td>
<td>↓sibutramine clearance, possible ↑toxicity (palpitations, etc)</td>
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<td></td>
<td>SSRI &amp; related antidepressants, MAOIs, sumatriptan &amp; related antimigraine drugs, dihydroergotamine, pethidine, pentazocine, fentanyl</td>
<td>Serotonin syndrome possible (diarrhoea, abdominal pain, ↑BP, tremors, hyper-reflexia, convulsions, etc) and/or increased risk of CNS toxicity</td>
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<tr>
<td></td>
<td>Antipsychotics</td>
<td>Increased risk of CNS toxicity</td>
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<tr>
<td></td>
<td>Sympathomimetics (eg pseudoephedrine, some cough/cold remedies)</td>
<td>Possible ↑BP. Avoid</td>
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GUIDELINES FOR THE USE OF SIBUTRAMINE AND ORLISTAT IN TAYSIDE
Summary and Recommendations

DIET & LIFESTYLE ADJUSTMENT
Requires close supervision and support from suitably trained personnel. Long-term compliance is ESSENTIAL.

REVIEW PROGRESS at 3 Months

NO WEIGHT LOSS or SOME WEIGHT LOSS but target not reached.

Is a further 3-month trial of diet/lifestyle change worth trying?

YES
Continue diet/lifestyle change

NO

WEIGHT LOSS equivalent to 5-10% or more of baseline body weight.

CONTINUE with diet & lifestyle advice and support.

Consider ANTI-OBESITY DRUG THERAPY
(based on available drugs, their action, side-effects precautions & contraindications).

ORLISTAT (XENICAL®)
Check contraindications/precautions. Counsel patient re: diet, side effects, etc.

REVIEW AT 3 MONTHS.
Discontinue treatment if:
Failure to lose 5% initial weight.

CONTINUE treatment for up to 24 months.

DISCONTINUE if 3-5kg weight regain after initial loss or BMI falls below 30 kg/m² (or below 27/28 kg/m² if co-morbid risk factors)

SIBUTRAMINE (REDUCTIL®)
Check contraindications/precautions. Counsel patient re: side effects etc.

REVIEW AT 3 MONTHS.
Discontinue treatment if:
Failure to lose 5% initial weight.

CONTINUE treatment for 12 months.

GOOD PRACTICE POINTS
Patients require monitoring and encouragement; consider prescribing no more than one month’s treatment.
Sibutramine: blood pressure and pulse rate MUST be monitored every two weeks for first three months. then monthly for three months. then at least every 3 months thereafter.

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