

**rimonabant 20mg tablet (Acomplia<sup>o</sup>)**

**No. (341/07)**

**Sanofi-Aventis**

12 January 2007

The Scottish Medicines Consortium has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**rimonabant (Acomplia<sup>o</sup>)** is not recommended for use within NHS Scotland as an adjunct to diet and exercise for the treatment of obese patients (body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>), or overweight patients (BMI  $>27$  kg/m<sup>2</sup>) with an associated risk factor or risk factors such as type 2 diabetes or dyslipidaemia.

Rimonabant was associated with a reduction in mean weight of about 4-5kg over that with placebo. However, this weight was generally regained within one year of stopping treatment. The economic case has not been demonstrated.

The licence holder has indicated their decision to resubmit.

Overleaf is the detailed advice on this product.

**Chairman  
Scottish Medicines Consortium**

**Indication**

As an adjunct to diet and exercise for the treatment of obese patients (BMI  $\geq 30$  kg/m<sup>2</sup>), or overweight patients (BMI  $>27$  kg/m<sup>2</sup>) with associated risk factor(s), such as type 2 diabetes or dyslipidaemia.

**Dosing information**

20mg daily

**Product availability date**

28 June 2006

**Summary of evidence on comparative efficacy**

Rimonabant is a selective cannabinoid-1 receptor (CB1) antagonist. It inhibits the effects of cannabinoid agonists within the endocannabinoid system present in the brain and peripheral tissues (including adipocytes), which affects energy balance, glucose and lipid metabolism and modulates the intake of highly palatable, sweet or fatty foods.

Two double-blind trials recruited 1508 and 3045 adults who were overweight (defined as a body mass index (BMI)  $>27$ kg/m<sup>2</sup>) and had hypertension and/or dyslipidaemia or were obese (defined as BMI  $\geq 30$ kg/m<sup>2</sup>). Patients underwent a 4-week single-blind placebo run-in period where they had a diet with approximately 600 calories per day less than required to maintain their weight and were encouraged to increase their physical activities. They continued this and were then randomised, with stratification by weight loss on restricted diet alone ( $\leq 2$ kg or  $>2$ kg), in a 1:2:2 ratio to double-blind placebo or rimonabant 5mg or 20mg once daily for one year. After one year, patients in the European study continued their allocated treatment for a further year and, in the North American study, patients in each rimonabant group were randomised in a 1:1 ratio to their allocated dose of rimonabant or placebo for a further year, with patients in the original placebo group continuing this in the second year. The primary outcome at one year was the mean reduction in body weight from baseline in the intention to treat (ITT) population, which included all patients treated with study drug who had a baseline and at least one post-baseline assessment, with last observations carried forward for missing data. This was significantly greater with the licensed dose of rimonabant, 20mg daily, compared to placebo in both studies: 6.6 vs. 1.8kg, with least square mean (95% confidence interval (CI)) effect over placebo of 4.7kg (3.8, 5.6) in the European study and 6.3 vs. 1.6kg, with a mean (95% CI) effect over placebo of 4.7kg (4.1, 5.4) in the North American study. In both studies rimonabant, compared to placebo, was associated with significantly greater proportions of patients achieving at least a 5% weight loss from baseline, approximately 50% vs. 20%, and achieving at least a 10% weight loss, 25-27% vs. 7-8%. In the second year of the North American study, the primary analysis investigated weight regain. During year two mean weight loss from baseline in the group that continued on rimonabant 20mg daily was maintained at two years. However, in the group treated with rimonabant 20mg in year one then placebo in year two, mean weight increased by the end of year two to the same level as the group that received placebo for both years. (Graphs, but not figures, were provided for the latter analyses).

Two double-blind trials recruited people aged 18-70 years who were overweight or obese (defined as BMI 27-40kg/m<sup>2</sup>), with one trial including only those with untreated dyslipidaemia (fasting triglyceride levels 1.7 to 7.9 mmol/L and/or a ratio of total cholesterol (TC) to high density lipoprotein cholesterol (HDL-C) of >4.5 units in women and >5.0 units in men) and the other trial including only those with type 2 diabetes who had not achieved adequate glycaemic control (HbA<sub>1c</sub> 6.5% to 10% and fasting glucose 5.55 to 15.04 mmol/L) despite at least 6 months' treatment with either metformin or sulphonylurea monotherapy. After a 4week single-blind placebo run-in period, as described for the previous studies, patients were randomised in a 1:1:1 ratio to placebo or rimonabant 5mg or 20mg once daily for one year, with stratification for weight loss on restricted diet alone ( $\leq$ 2kg or >2kg), and by triglyceride level ( $\leq$ 4.5 mmol/L or >4.5 mmol/L) in the first study and, in the second study, by anti-diabetic medication (metformin or sulphonylurea). The primary outcome was the same as that in the two studies described previously and was significantly greater with the licensed dose of rimonabant, 20mg daily, compared to placebo in both studies: 6.9 vs. 1.5kg, with least square mean (95% CI) effect over placebo of 5.4kg (4.6, 6.2) in the first study and 5.3 vs. 1.4kg, with a mean (95% CI) effect over placebo of 3.9kg (3.3, 4.6) in the second study. In both studies rimonabant, compared to placebo, was associated with significantly greater proportions of patients achieving at least a 5% weight loss from baseline, 58% vs. 20% and 49% vs. 14% in the respective studies, and achieving at least a 10% weight loss, 33% vs. 7.2% and 16% vs. 2.0% in the respective studies.

### **Lipid profile**

Obesity is often associated with low serum concentrations of HDL-C and high concentrations of triglycerides. In all of the trials described previously rimonabant 20mg daily, compared to placebo, was associated with significantly greater mean percent increases from baseline to year one in HDL-C, with treatment effects over placebo of 7.2% to 8.4%. Similarly, in all of the studies rimonabant 20mg was associated with decreases from baseline to year one in triglycerides, which were significantly different from increases or stable levels in the placebo groups, with treatment effects over placebo of 12% to 16%. However, in the North American trial triglycerides increased and HDL-C decreased in year two within the group that had received rimonabant 20mg in year one and placebo in year two.

### **Glycaemic control**

In the trial that recruited patients with type 2 diabetes, rimonabant 20mg daily, compared to placebo, was associated with a mean decrease in HbA<sub>1c</sub> from baseline to year one of 0.6% that was significantly different from the 0.1% increase in the placebo group. This corresponds to a mean (95% CI) treatment effect over placebo of 0.7% (0.5% to 0.8%). Mean reductions from baseline to year one in insulin resistance and fasting plasma glucose were significantly greater with rimonabant 20mg compared to placebo, with a mean (95% CI) treatment effect over placebo for fasting glucose of 0.97 mmol/L (1.30, 0.64).

### **Quality of life**

In pooled data from the trials described previously, there were significant improvements with rimonabant 20mg daily compared to placebo in the total score of the Impact of Weight on Quality of Life-Lite (IWQOL-Lite) questionnaire, all five of its domains (physical functioning, self-esteem, sexual life, public distress and work) and on the physical function and general health scores of the short-form (SF-36). However, there was a significant deterioration in the SF-36 mental health score with rimonabant 20mg daily compared to placebo.

## Summary of evidence on comparative safety

The most common adverse effects with rimonabant were psychiatric and gastrointestinal. In pooled one-year data from the four trials described previously the following adverse effects within these classes were more frequently reported with rimonabant 20mg than placebo: nausea (12% vs. 4.9%), diarrhoea (6.3% vs. 4.8%), vomiting (4.0% vs. 2.2%), anxiety (5.6% vs. 2.4%), insomnia (5.4% vs. 3.2%), mood disorder with depressive symptoms (4.8% vs. 3.1%), depressive symptoms (3.2% vs. 1.6%), irritability (1.9% vs. 0.6%), parasomnia (1.5% vs. 0.2%), nervousness (1.2% vs. 0.2%) and sleep disorders (1.0% vs. 0.4%).

## Summary of clinical effectiveness issues

Reduction of obesity may be associated with reductions in risks of obesity-related conditions such as cardiovascular disease and type 2 diabetes. However, there are no trials that have shown reductions in morbidity or mortality with a weight-loss treatment. The European regulatory authority considers a reduction of at least 10% in weight from baseline is clinically significant and in the trials described previously rimonabant was associated with this in about 15-25% more patients than placebo. Mean weight reduction with rimonabant reached a plateau at about 36 weeks. However, in the North American study, which was designed to investigate weight regain upon stopping rimonabant, mean weight increased from the point at which it was discontinued and within one year had reached the same level as the group who had not received the drug, with benefits on triglycerides and HDL-C also reversing during this time. The Summary of Product Characteristics for rimonabant notes that efficacy and safety beyond two years have not been studied. In practice where rimonabant is given for a maximum of two years, it may be associated with weight reductions of less than 10% in the majority of patients, with patients generally regaining their lost weight within one year of discontinuing the drug. The clinical significance of these short-term weight effects on long-term outcomes, such as cardiovascular disease and type 2 diabetes, are unknown.

The trials described previously excluded patients with a history of severe depression or any current serious psychiatric condition, including major depression. Pooled data indicate that at baseline the majority of patients (92%) had a normal score of  $\leq 7$  on the depression subscore of the Hospital Anxiety and Depression scale, with 6.7% having a score of 8-10, suggestive of borderline depressive symptoms and less than 2% having a score  $\geq 11$ , suggesting significant symptoms. Obesity is often associated with depression and other psychiatric conditions. However, there are limited data on the safety of rimonabant, which is associated with psychiatric adverse effects such as anxiety and depression, in patients with depression or psychiatric conditions.

There are no trials comparing rimonabant with the other drugs, orlistat and sibutramine, which are licensed for the treatment of obesity and have been recommended by the National Institute for Health and Clinical Excellence (NICE). Thus, efficacy and safety of rimonabant relative to these drugs are unknown. The NICE health technology assessments of orlistat and sibutramine note that at one year they are associated with mean weight reductions over those with placebo of 25kg and 4-5kg, respectively. These are similar to those observed with rimonabant. NICE also noted that on average it appears to take three years to regain the weight lost that has been lost over a year on orlistat and sibutramine, although, it was noted for orlistat that there was uncertainty around this figure. Two of the double-blind trials included in the NICE health technology assessment of orlistat had a similar methodology to the North American rimonabant study. They randomised obese (BMI 30-43kg/m<sup>2</sup> in the first study and 28-47kg/m<sup>2</sup> in the second study) non-diabetic adults to placebo or the licensed dose or

orlistat for a year. Then patients in the orlistat groups were re-randomised to placebo or orlistat for year two. Mean weight losses with orlistat over placebo at one year were 3kg and 4kg in the respective trials. However, in orlistat-treated patients randomised to placebo in year two, mean weight had increased by the end of year two to the same level as the group that received placebo for both years in the first study and in the second study to a level slightly below that of the placebo group. These weight regains appear similar to those with rimonabant in the North American trial.

In the trials described previously, which recruited patients with type 2 diabetes who had not achieved adequate glycaemic control despite treatment one anti-diabetic drug and who had untreated dyslipidaemia, these conditions were not subsequently treated during the one-year studies. In practice, inadequately controlled diabetes and would be treated with the addition of another anti-diabetic medication and drug therapy, for example a statin, would be used to treat dyslipidaemia. Therefore, the benefits on blood glucose control (HbA<sub>1c</sub>), HDL-C and triglycerides with rimonabant relative to placebo in these trials may not be relevant to Scottish practice.

## **Summary of comparative health economic evidence**

The manufacturer submitted a cost-utility analysis comparing rimonabant plus diet-and-exercise advice to diet-and-exercise advice alone. A second analysis used orlistat as the comparator. A Markov model was used based on data from clinical trials of rimonabant and orlistat supplemented by data from published research studies on the long-term consequences of changing risk factor levels.

In the base-case analysis (where 7% of patients have diabetes and 0% dyslipidaemia) the manufacturer estimated adding rimonabant to diet and exercise would result in a cost per quality adjusted life year (QALY) of £10,991. For patients with dyslipidaemia the addition of rimonabant to diet-and-exercise would result in a cost per QALY of £10,120 compared to diet-and-exercise alone and £9,186 compared to orlistat. For patients with diabetes, the manufacturer estimated that the cost per QALY would be £13,653 compared to diet-and-exercise alone and £10,491 compared to orlistat.

The economic evaluation enabled cost-effectiveness to be assessed against orlistat and against lifestyle changes; however, the comparator offered no active treatment for diabetes or dyslipidaemia, which seems at odds with normal prescribing practice. Given that an inappropriate comparator has been used it is difficult to assess incremental cost-effectiveness.

The manufacturer used a wide variety of risk equations and the selections made were not always clearly explained: for example, Canadian data were used to estimate survival after a cardiovascular event but it is not clear whether this is representative of Scotland or whether the data relate specifically to the types of patients eligible for rimonabant. The resource use involved in hospital treatments was generally not made clear so a cost was attached to each adverse event but the resource use involved was not set out.

The economic case has not been demonstrated primarily because it was not clear the comparator reflected current practice.

## **Summary of patient and public involvement**

A Patient Interest Group Submission was not made.

## Additional information: guidelines and protocols

The November 1996 Scottish Intercollegiate Guidelines Network (SIGN) guideline number 8 on obesity: integrating prevention with weight management predates the licensing of drugs in the UK for the treatment of obesity and therefore makes no recommendations on these.

The December 2006 NICE obesity guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children notes that drug treatment should be considered for patients who have not reached their target weight loss or have reached a plateau on dietary, activity and behavioural changes alone. Prescribing should be in accordance with the drug's summary of product characteristics. Pharmacological treatment may be used to maintain weight loss, rather than continue to lose weight. Regular review is recommended to monitor the effect of drug treatment and to reinforce lifestyle advice and adherence. Withdrawal of drug treatment should be considered in people who do not lose enough weight. Rates of weight loss may be slower in people with type 2 diabetes, so less strict goals than those for people without diabetes may be appropriate. These goals should be agreed with the person and reviewed regularly. Orlistat should be prescribed only as part of an overall plan for managing obesity in adults who meet one of the following criteria: BMI of 28kg/m<sup>2</sup> or more with associated risk factors; or BMI of 30kg/m<sup>2</sup> or more. Therapy should be continued beyond 3 months only if the person has lost at least 5% of their initial body weight since starting drug treatment. The decision to use drug treatment for longer than 12 months (usually for weight maintenance) should be made after discussing potential benefits and limitations with the patient. Sibutramine should be prescribed only as part of an overall plan for managing obesity in adults who meet one of the following criteria: BMI of 27kg/m<sup>2</sup> or more and other obesity-related risk factors such as type 2 diabetes or dyslipidaemia; or BMI of 30kg/m<sup>2</sup> or more. Sibutramine should not be prescribed unless there are adequate arrangements for monitoring both weight loss and adverse effects (specifically pulse and blood pressure). Therapy should be continued beyond 3 months only if the person has lost at least 5% of their initial body weight since starting drug treatment. Treatment is not currently recommended beyond the licensed duration of 12 months.

## Additional information: comparators

Orlistat, a gastrointestinal lipase inhibitor, and sibutramine, an inhibitor of noradrenaline, serotonin and dopamine reuptake, are both licensed for the same indication as rimonabant. Both of these drugs have been recommended by NICE for the management of obesity.

## Additional information: costs

Drug	Dose range	Annual cost (£)
Rimonabant	20mg once daily	720
Sibutramine	10-15mg once daily	592-647
Orlistat	120mg with each main meal (up to three times daily)	515

Doses are shown for general comparison and do not imply therapeutic equivalence

## **Additional information: budget impact**

The manufacturer requested that the budget impact information remain commercial in confidence.

*Other data were also assessed but remain commercially confidential.\**

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*

*This assessment is based on data submitted by the applicant company up to and including 3 January, 2007.*

*Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.*

*\* Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: <http://www.scottishmedicines.org.uk/>*

*The undernoted references were supplied with the submission.*

*Pi-Sunyer FX, Aronne LJ, Heshmati HM et al. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients. RIO-North America: a randomized controlled trial. JAMA 2006; 295: 761-75.*

*Van Gaal LF, Rissanen AM, Scheen AJ et al. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. Lancet 2005; 365:1389-97.*

*Despres J-P, Golay A, Sjostrom L. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. N Engl J Med 2005; 353: 2121-34.*

*Davidson MH, Hauptman J, DiGirolamo M et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomised controlled trial. JAMA 1999; 281: 235-42.*

*Sjostrom L, Rissanen A, Andersen T et al. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. Lancet 1998; 352: 167-73.*