

Pharmacotherapeutic report rimonabant (Acomplia®) for the indication obesity

1. Summary

The Medicinal Products Reimbursement Committee (CFH) has approved the pharmacotherapeutic report for the drug rimonabant (Acomplia®), tablet, coated, 20 mg. In order to determine its therapeutic value, it was compared with diet and physical exercise, as well as with two other drugs registered for use in cases of obesity or excess weight with related risk factors: orlistat (Xenical®) and sibutramin (Reductil®). They reached the following conclusions:

Rimonabant is a selective cannabinoide-1 (CB1) receptor-antagonist, registered as a supplement to diet and physical exercise for the treatment of patients with obesity (BMI ≥ 30 kg/m²), or patients with excess weight (BMI > 27 kg/m²) in combination with risk factor(s), such as type 2 diabetes or dyslipidemia.

Diet and physical exercise are the most important cornerstones to the treatment of excess weight and obesity. If these treatments yield insufficient results, there may be a role for drugs. The efficacy of such weight-reducing drugs is limited. After one year of taking rimonabant, under optimal guidance, the average weight loss was approximately 5 kg (about 5%) in comparison with placebo. This reduction is comparable with what is achieved by sibutramin and it exceeds what has been achieved by orlistat. Furthermore, the use of rimonabant has a favourable effect on a number of cardiovascular risk factors, such as increasing HDL cholesterol and reducing the level of triglycerides, and reducing waist measurement. In patients with type 2 diabetes mellitus, as a supplement to monotherapy with metformin or a sulphonylureum derivative, a 0.7% reduction is found in the HbA1c level in comparison with placebo. However, it is not clear whether the patients were maximally adjusted to oral blood-sugar-reducing drugs.

Rimonabant treatment appears to yield greater improvements in various risk factors for heart and vascular disease than sibutramin and orlistat usage. However, these are secondary endpoints in the published studies. Moreover, effective drugs with a favourable effect on the lipids and glucose metabolism are available. These drugs have been proven to reduce the risk of diabetic and cardiovascular complications and mortality, whilst no such positive effect has been established for weight-reducing drugs such as rimonabant.

Approximately 40-50% of the patients taking rimonabant terminate treatment prematurely; though these termination percentages are common in studies involving patients with obesity, they do hamper interpretation of the results. After termination, any reduction in body weight will largely be undone. With rimonabant the depressive disorders are most likely to lead to termination of treatment, with orlistat the side effects on the gastrointestinal canal will lead to termination, and with sibutramin the cardiovascular side effects (tachycardia) will cause termination.

Final conclusion on therapeutic value

When used to treat obesity, rimonabant has a therapeutic value comparable to that of sibutramin. Moreover, the Committee has already concluded that sibutramin should not be used in obesity treatment.

Rimonabant has no therapeutic added value in comparison with diet and physical exercise. No positive effect has been demonstrated on cardiovascular and diabetic complications and mortality. Moreover, there is a lack of long-term data. A large proportion of the patients cease treatment prematurely, partly based on the side effects. In spite of indications of a positive effect on weight and glycaemic status, currently no therapeutic added value has been demonstrated for the subgroup of patients with excess weight and type 2 diabetes mellitus. As a result the Committee does not envisage a place for rimonabant.

2. Introduction

Drug	Acomplia®
Composition	Rimonabant. Tablet, coated 20 mg.

Registered indication	As adjuvant to diet and physical exercise for the treatment of patients with obesity (BMI ≥ 30 kg/m ²), or patients with excess weight (BMI > 27 kg/m ²) in combination with risk factor(s), such as type 2 diabetes or dyslipidemia.
Dose	<i>Adults:</i> In combination with a light hypocaloric diet: once daily 20 mg before breakfast.
Mode of action	Selective cannabinode-1 (CB1) receptor antagonist. The endocannabinoid system is a physiological system that is present in the brains and peripheral tissues (incl. adipocytes). It affects the energy balance, the metabolism of glucose and lipids and body weight, and affects the uptake of foodstuffs.
Specific details	

For extensive information on the drug, please consult the product text that is to be published in the next issue of the *Farmacotherapeutisch Kompas* (see appendix 1).

3. Starting points for the assessment

3.a. Therapeutic area

The prevalence of excess weight (BMI 25-30 kg/m²) and obesity (BMI ≥ 30 kg/m²) is increasing. On average, the body weight of 40% of the Dutch population is excessive; 10% of the adult population suffers from obesity. The risk of co-morbidity increases as the BMI increases, whereby it is not only the absolute quantity of fat that is important, but also the fat distribution. Intra-abdominal fat leads to a higher risk of disease than subcutaneous fat that is localised peripherally, for example, around the hips. Measuring the waist circumference gives an impression of the quantity of intra-abdominal fat. The risk is seriously increased with a waist measurement of 94-102 cm in men and 80-88 cm in women.¹

One of the consequences of weight increase is insulin resistance, whereby the normal working of insulin is disrupted. Insulin resistance plays a key role in developing the so-called metabolic syndrome. This syndrome is characterised by a cluster of metabolic and haemodynamic defects such as abdominal obesity, increased blood pressure, (slightly) raised values for blood-sugar and insulin, increased triglyceride values and reduced HDL cholesterol values. These defects contribute to the development of heart and vascular disease, type 2 diabetes mellitus and the complications these involve, gall stones and possibly some forms of cancer. There is no generally accepted definition of the metabolic syndrome.^{2 3 4} The metabolic syndrome can be regarded as a combination of individual risk factors. Most people with the metabolic syndrome are eligible for determining the risk of heart and vascular diseases according to the criteria as described in the CBO standard cardiovascular risk management. If the risk factors are subsequently treated, this leads to a considerable reduction in the number of heart and vascular diseases. Therefore, there is little added value in specifically distinguishing patients with the metabolic syndrome within the framework of cardiovascular risk management.^{5 6}

The increased prevalence of excess weight and obesity can probably be blamed on an increasing lack of activity, in combination with relative excessive consumption. Based on the study results available, a diet with a low energy density, i.e., with a lot of vegetables, fruit and cereal products, provides the best guarantee for maintaining the energy balance. Moderate daily exercise (at least one hour of moderate physical activity per day) would seem to be more important for preventing an increase in body weight than a single peak load. Genetic factors do play a role in the development of excess weight and obesity. Nevertheless, the effect of environmental factors seems to be the decisive factor.⁷

The body mass index (BMI) and fat distribution are involved in the decision of whether a patient is eligible for treatment of excess weight. According to treatment guidelines proposed in the Netherlands, treatment is always indicated for a BMI of 30 kg/m² or higher. Persons with a BMI of

25-30 kg/m² are eligible for treatment when their waist measurement is increased or where 2 or more other risk factors are present.¹

In most cases, the treatment of excess weight and obesity should focus on moderate weight loss, circa 10% of the original weight. In addition, long-term maintenance of this weight loss and treatment of the co-morbidity are important gauges for treatment. For the moment, there is a lack of prospective studies demonstrating that moderate weight loss leads to fewer heart and vascular diseases and/or to reduced mortality. An observational study did demonstrate a correlation between loss of weight and a reduction in total mortality among the 4970 patients with excessive weight and diabetes. However, there is a lack of information about the method of weight loss in this study.⁸

Excess weight treatment is based on responsible dietary advice, exercise and behaviour. A multi-disciplinary approach by the G.P./doctor, dietician, physiotherapist and behavioural therapist is hereby preferred.

In cases of severe, morbid obesity, surgery may be a treatment option.

In all chosen treatment strategies, it is clear that patients are often unsuccessful in achieving permanent weight loss. Moreover, hardly any research has been done regarding the efficacy of long-term treatment in preventing a return to the previous weight.

In view of the frequently disappointing results of treatment and the great efforts necessary to retain a certain weight loss, the report of the National Health Council claims that in attempting to reduce the prevalence of excess weight and obesity, the emphasis should be switched to prevention.⁷

3.b. Choice of comparative treatment

Two drugs are registered for the medicinal treatment of excess weight/obesity: orlistat and sibutramin. Rimonabant needs to be compared with these. These drugs are used as adjuvant to a hypocaloric diet and physical exercise. Orlistat selectively inhibits the lipases from the pancreas and the intestines and reduces the resorption of fat in the intestines. The appetite inhibitor sibutramin affects the feeling of satiation (via serotonin) and raises metabolism in rest (via noradrenalin). An average reduction in body weight of about 3 kg (\pm 3%) is achieved with orlistat, and a reduction of 4-5 kg (about 5%) with sibutramin. At the same time, the use of orlistat led to small improvements in total cholesterol and LDL cholesterol values, blood pressure and glycaemic control; however, the HDL cholesterol level was slightly reduced. With sibutramin there was a small improvement in HDL cholesterol and triglyceride values, whilst there was a small increase in blood pressure.^{9 10} The efficacy and safety data for orlistat will be available in four years' time. However, for the moment, the Committee sees no place for orlistat, because weight reduction is extremely limited (<5%). Nor is there a place for sibutramin in treating obesity, because the drug can only be used for one year and weight gain occurs once therapy is stopped.

3.c. Method of assessment

For the assessment, preference goes out to using the IB text of the registration file, the EPAR/NPAR and direct comparative research that has been published in peer-reviewed journals. On 8th January 2007 a literature search was carried out on the most recent files of Med-line, Embase and Cochrane. The following search terms were used: rimonabant, anti-obesity drugs, orlistat, sibutramin. This led to supplementing the file with two review articles (Kishore et al., Circulation 2006; 114:974-84; Padwal et al., Lancet 2007; 369:71-7).

4. Therapeutic value

The therapeutic value of rimonabant was assessed according to the criteria efficacy, effectiveness, side effects, quality of life, experience, applicability and ease of use.

4.a. Efficacy/effectiveness

Efficacy was assessed according to the degree of weight loss; effectiveness was assessed on the basis of reducing morbidity and mortality in relation to excess weight.

There is a lack of comparative research between rimonabant and orlistat or sibutramin.

Four randomised, double-blind studies have been carried out in which rimonabant (5 mg/day or 20 mg/day) was compared with placebo: RIO-Europe, RIO-Lipids, RIO-North America and RIO-Diabetes. These studies included patients with a BMI ≥ 30 kg/m² or a BMI >27 kg/m², and with dyslipidemia (high triglyceride or low HDL cholesterol values), type 2 diabetes mellitus or hypertension. Throughout these studies, the patients followed a restricted diet that was prescribed by a dietician (mildly hypocaloric diet: -600 kcal/day). In addition they were advised to increase physical exercise.

Approximately 80% of the research population was made up of women, 87% of the Caucasian race and 9% from the Negroid race. The most important results are presented in table 1.

The primary endpoint in these studies was the alteration in body weight after one year's treatment. Secondary endpoints included waist measurement, HbA1c level, HDL cholesterol and triglyceride values and prevalence of the metabolic syndrome.

There were important exclusion criteria in the RIO studies: cardiovascular or pulmonary diseases, disorders in the liver or renal function, as well as neurological or psychiatric diseases; the presence of type 1 or type 2 diabetes mellitus was also included in the RIO-Europe, -Lipids and -North-American studies.

The results of the RIO-studies were analysed in the intention-to-treat population according to the principle "last observation carried forward". The assumption here was that after dropping out from the study, the patient would no longer experience any further weight loss. This hampers interpretation of the results.

As 20 mg per day is the registered dose, the results with rimonabant 5 mg/day were not mentioned in this report.

RIO-Europe ¹¹

In this study 1507 patients (with a BMI ≥ 30 kg/m² or a BMI >27 kg/m² and with dyslipidemia and/or hypertension) were randomised into treatment with placebo (n=305), 5 mg (n=603) or 20 mg rimonabant (n=599) per day.

At the start of the study, the average body weight was 101 kg, about 41% had hypertension, about 61% had dyslipidemia and about 41% complied with the definition of the metabolic syndrome.

Weight loss when treated with rimonabant 20 mg/day (-6.6 kg [SD 7.2]; $p < 0.001$) was significantly greater in comparison with treatment with placebo (-1.8 kg [SD 6.4]). This also applied to the reduction in the waist measurement (-6.5 cm [SD 7.4] vs -2.4 cm [SD 6.9]; $p < 0.001$).

Significantly more patients in the rimonabant 20-mg leg than in the placebo leg achieved a weight loss of more than 5% (67 vs 31%; $p < 0.001$) or 10% (27 vs 7%; $p < 0.001$).

In the rimonabant 20-mg leg the improvement in the HDL cholesterol value (+22.3 [SD 0.9] vs +13.4 [SD 1.1]; $p < 0.001$) and the triglyceride value (-6.8 [SD 1.5] vs +8.3 [SD 2.6]; $p < 0.0001$) was significantly greater than in the placebo leg.

The percentage of persons that met the criteria for the metabolic syndrome (NCEP-ATPIII) dropped from 41% to about 20% in the rimonabant 20-mg leg and to about 31% in the placebo leg (significant difference; $p < 0.001$).

Pharmacotherapeutic report Rimonabant (Acomplia®)

The study had a high dropout rate: 61% were followed up for 1 year, 58.4% in the placebo group, and 60.6% being administered rimonabant 20 mg.

RIO-Lipids ¹²

This study included 1036 patients with a BMI of 27-40 kg/m² and untreated dyslipidemia (fasting triglyceride values: 1.7-7.9 mmol/l and/or total cholesterol/HDL cholesterol ratio >5 [for men] or >4.5 [for women]).

Weight loss when treated with rimonabant 20 mg/day (-6.9 kg [SD 6.1]; p<0.001) was significantly higher in comparison with placebo (-1.5 kg [SD 5]). This also applied to the reduction in waist measurement (-7.1 cm [SD 6.8] vs -2.4 cm [SD 5.7]; p<0.001).

Significantly more patients in the rimonabant 20-mg leg than in the placebo leg achieved a weight loss of more than 5% (58.4 vs 19.5%; p<0.001) or 10% (32.6 vs 7.2%; p<0.001).

In the rimonabant 20-mg leg, the improvement in the HDL cholesterol value (+19.1% [SD 20.9] vs +11.0% [SD 15.8]; p<0.001) and the triglyceride value (-12.6% [SD 41.2] vs -0.2% [SD 38.7]; p<0.001) was significantly greater than in the placebo leg.

The percentage of that met the criteria of the metabolic syndrome (NCEP-ATPIII) decreased from 54% of the patients to 25.8% in the rimonabant 20-mg leg and to 41% in the placebo leg (significant difference; p<0.001). This was particularly related to the reduction in the waist measurement and the increase in the HDL cholesterol values.

The study had a high dropout rate: 62.6% of the patients in the placebo group and 63.9% in the rimonabant 20-mg group completed the study.

RIO-North America ¹³

In this study 3045 patients (with a BMI ≥ 30 kg/m² or a BMI >27 kg/m², and with dyslipidemia and/or hypertension) were randomly divided into treatment with placebo or rimonabant in addition to a mildly hypocaloric diet (-600 kcal/day).

Weight loss was significantly greater when treated with rimonabant 20 mg/day (-6.3 kg [SD 0.2]; p<0.001) in comparison with placebo (-1.6 kg [SD 0.2]). This also applied to the reduction in waist measurement (-6.1 cm [SD 0.2] vs -2.5 cm [SD 0.3]; p<0.001).

Significantly more patients in the rimonabant 20-mg leg than in the placebo leg achieved a weight loss of more than 5% (48.6 vs 20%; OR 4.1 [95%CI: 3.2-5.2]; p<0.001) or 10% (25.2 vs 8.5%; OR 4.0 [95%CI: 2.9-5.5]; p<0.001).

In the rimonabant 20-mg leg the improvement in the HDL cholesterol value (+12.6% [SD 0.4] vs +5.4% [SD 0.7]; p<0.001) and triglyceride value (-5.3% [SD 1.2] vs 7.9% [SD 2.0]; p<0.001) was significantly greater than in the placebo leg.

The study had a high dropout rate: only 51% of the patients in the placebo group and 55% in the rimonabant 20-mg group completed the study.

After 1 year the test subjects who had received 20 mg/day rimonabant for one year received - at random - either 20 mg/day rimonabant or a placebo. After two years the patients who continued to use rimonabant had a total weight loss of 7.4 (0.4) kg in comparison with baseline, whilst the weight loss booked in patients who received placebo was as good as cancelled. The positive effect on the lipids also continued throughout the second year that rimonabant was taken.

RIO-Diabetes ¹⁴

In this study 1054 patients with type 2 diabetes mellitus were randomised into treatment with placebo (n=348), rimonabant 5 mg/day (n=358) or rimonabant 20 mg/day (n=339) during 1 year. Inclusion criteria were a BMI of 27-40 kg/m² (average weight 98 kg), a HbA1c level between 6.5 and 10% and a fasting blood-sugar level between 5.55 and 15.05 mmol/l. Prior to the study, the

patients were treated with metformin or sulphonylureum derivatives as monotherapy for at least 6 months.

The weight loss when treated with rimonabant 20 mg/day (-5.3 kg [SD 5.2]; $p < 0.0001$) was significantly greater in comparison with placebo (-1.4 kg [SD 3.6]). This also applied to the reduction in waist measurement (-5.2 cm [SD 6.1] vs -1.9 cm [SD 5.5]).

Significantly more patients in the rimonabant 20-mg leg than in the placebo leg achieved a weight loss of more than 5% (49.4 vs 14.5%; $p < 0.0001$) or 10% (16.4 vs 2%; $p < 0.0001$).

In the rimonabant 20-mg/day leg, the HbA1c level dropped by 0.6% [SD 0.8] in comparison with an increase of 0.1% [SD 1.0] in the placebo leg ($p < 0.0001$). The fasting blood-sugar level fell by 0.64 mmol/l [SD 1.96] in the rimonabant 20 mg/day leg, in comparison with an increase of 0.33 mmol/l [SD 2.32] in the placebo leg.

This study also had a high dropout rate: 66.2% had a 1-year follow-up.

Table 1. Placebo-controlled research with rimonabant

Study, duration	Drug	N	Weight (kg)	HDL Cholesterol (% change)	Triglycerides	HbA1c (% change)
RIO Europe 1 year	Rimonabant 20 mg Placebo	599 305	-6.6 ± 7.2 -1.8 ± 4.6	+22.3 ± 0.9 +13.4 ± 1.1	- 6.8 ± 1.5 +8.3 ± 2.6	
RIO-Lipids 1 year	Rimonabant 20 mg Placebo	346 342	-6.9 ± 6.1 -1.5 ± 5	+19.1 ± 20.9 +11.0 ± 15.8	- 2.6 ± 41.2 - 0.2 ± 38.7	
RIO-North America 1 year (extended to 2 years, results not included in table)	Rimonabant 20 mg Placebo	1222 607	-6.3 ± 0.2 -1.6 ± 0.2	+12.6 ± 0.4 + 5.4 ± 0.7	- 5.3 ± 1.2 +7.9 ± 0.2	
RIO-diabetes	Rimonabant 20 mg Placebo	339 348	-5.3 ± 5.2 -1.4 ± 3.6	+15.4 ± 17.4 + 7.1 ± 13.5	- 9.1 ± 44.3 +7.3 ± 43.0	- 0.6 ± 0.8 + 0.1 ± 1.0

Discussion:Weight control

In the three studies carried out on non-diabetic patients, significantly greater average weight losses (6.5 vs 1.6 kg) from baseline to one year were demonstrated with rimonabant 20 mg/day than with placebo (difference -4.9 kg [95%CI: -5.3;-4.4]; p<0.001).

The number of test subjects who had lost 5% and 10% of their baseline body weight after 1 year in the rimonabant 20-mg/day leg versus the placebo leg was resp. 50.8% versus 19.7% (difference 31.1% [95% CI:28%; 34%]) and 27% versus 7.8% (difference 19.2% [95% CI:17%; 22%]).¹⁵

In the study with type 2 diabetes mellitus patients, after one year an average weight loss of 5.3 kg was demonstrated for rimonabant 20 mg/day in comparison with a loss of 1.4 kg (difference -3.9 kg [95% CI: -4.6;-3.3]; p<0.001) with placebo.

The number of test subjects who after 1 year had lost 5% and 10% of their baseline body weight in the rimonabant 20-mg/day leg versus the placebo leg was resp. 49.4% versus 14.5% (difference 34.9% [95% CI:28%; 41%]) and 16.2% versus 2% (difference 14.2% [95% CI:10%; 19%]).¹⁸

The largest proportion of the weight loss observed was achieved within the first nine months of treatment. With rimonabant 20 mg/day, the weight loss was effectively maintained for up to two years. After 2 years the weight loss was 5.1 kg for patients who received rimonabant 20 mg/day and 1.2 kg with placebo (difference -3.8 kg; [95%CI:-4.4, -3.3]; p<0.001).

Additional risk factors

In the three studies carried out among non-diabetic patients (incl. patients with dyslipidemia), an increase in the HDL cholesterol value and a reduction in the triglyceride level was observed after 1 year. In the rimonabant 20-mg/day leg, an average increase of 16.4% (baseline 1.24 mmol/l) was observed, in comparison with an increase of 8.9% for placebo (baseline 1.21 mmol/l). The difference was significant (difference 7.9% [95% CI: 6.6%, 9.2%]; p<0.001). With respect to the triglyceride level, a significant improvement was also observed in the rimonabant 20-mg/day leg in comparison with the placebo leg: a reduction of 6.9% (baseline 1.62 mmol/l) in comparison with 5.8% (baseline 1.65 mmol/l). A difference of -13.3% [95%CI: 16.5%, -10.2%]; p<0.001). In general rimonabant had no significant effect on the total concentration or the LDL-cholesterol level.

An improvement in the HbA1c level was observed in the study involving type 2 diabetes mellitus patients with excess weight or obesity, and who were treated with metformin or a sulphonylureum derivative. The absolute difference after 1 year's treatment was -0.6 for rimonabant 20 mg/day (baseline 7.2%) and +0.1% with placebo (baseline 7.3%). The differences were statistically significant: difference -0.7% [95%CI: -0.80, -0.5]; p<0.001). However, it is not possible to determine from the study whether the patients investigated were receiving optimal treatment with the oral blood-sugar lowering drugs. Weight loss and an improvement in the glycaemic status are potentially positive for patients with type 2 diabetes mellitus. However, up till now there is no evidence that the use of rimonabant among these patients leads to a reduction in long-term

complications. Such a positive effect has been demonstrated for metformin and the sulphonylureum derivatives.

The alterations in the HDL cholesterol level and triglycerides were, for the rest, comparable with those in the non-diabetic population.

The improvements in the HDL cholesterol and the triglyceride level observed, and the HbA1c level of patients receiving 20 mg/day rimonabant, are estimated to be 50% more than what would be expected on the grounds of weight loss alone.¹⁶

Conclusion:

With optimum guidance, after using rimonabant for one year, in comparison with placebo, one can speak of an average reduction in body weight of circa 5 kg (about 5%). The clinical relevance of this is not clear. This reduction is comparable with that achieved with sibutramin and greater than what is achieved with orlistat. In addition, rimonabant has a positive effect on a number of cardiovascular risk factors, although these are secondary endpoints. These improvements seem to be greater with rimonabant than those achieved with sibutramin and orlistat, but no comparative research has been done. There is no evidence that using weight-reducing drugs such as rimonabant has a positive effect on (diabetic) complications and mortality. One must bear in mind that effective drugs are available that have a favourable effect on the lipids and glucose metabolism, and which have been proven to reduce the risk of (new manifestations of) heart/vascular diseases.

About 40-50% of the patients with rimonabant cease therapy prematurely; whilst these dropout percentages are normal for studies involving patients with obesity, they do hamper interpretation of the results.

4.b. Side effects

About 16% of the patients terminated treatment with rimonabant during placebo-controlled studies due to side effects. The side effects that occurred most frequently and which led to termination of treatment are nausea, altered moods, depressive disorders, anxiety and dizziness. The depressive disorders, mentioned by about 3% of the patients, were mild to moderately severe. Termination of treatment led to recovery.¹⁸

Note that patients with psychiatric disorders were excluded from the studies, hence it is possible that potential psychiatric side effects were underestimated.

The side effects that occurred most frequently in the studies with rimonabant, and which occurred in more than 5% of the patients, were: infection in the upper airways, nausea, diarrhoea, vomiting, dizziness, mood alteration, hypoglycaemia, arthralgia, tiredness and anxiety.

Discussion: Orlistat leads predominantly to local side effects related to the increased level of fat in the faeces, especially during the first year of treatment: fatty, oily stools and more frequent defecation occur most frequently (in 15-30%). In addition, 7% experience faecal incontinence, particularly at the start of treatment.

The side effects that occur most frequently when using sibutramin are tachycardia, sleep disorders, nausea, dry mouth and constipation.

Conclusion: studies with weight-reducing drugs have a high dropout rate, partly due to the side effects. Depressive disorders are the main cause of ceasing treatment with rimonabant, side effects on the gastrointestinal canal with orlistat and cardiovascular side effects (tachycardia) with sibutramin).

4.c. Experience

A total of more than 6800 patients were included in the phase II and III clinical studies. 2503 patients were treated with 20 mg rimonabant in the RIO-study programme. Since July 2006 rimonabant has been phased onto the market in England, Ireland, Germany and Denmark.

Discussion: Sufficient experience has been obtained with orlistat and sibutramin.

Conclusion: Experience with rimonabant is limited.

4.d. Applicability

Rimonabant should not be used in cases of severe liver or renal insufficiency as (sufficient) data regarding such application are not available. Furthermore, rimonabant should not be used in the event of a severe, uncontrolled psychological disorder such as a severe depression. Treatment can only be considered once this psychological disorder is controlled. Using rimonabant in combination with antidepressant medication is not recommended due to the limited amount of data available on such use in these patients.

Efficacy and safety for patients older than 75 years and younger than 18 year have not been sufficiently established.

Caution is warranted in combination with strong CYP3A4 inhibitors because these can strengthen the effect of rimonabant.

No data are available on use during pregnancy and lactation.

Patients who had suffered a cardiovascular incident (heart infarction, stroke, etc.) during the past six months were excluded from the studies with rimonabant. Patients with psychological disorders, particularly depressive disorders, were also excluded.

The safety and efficacy of rimonabant have not been studied for longer than 2 years.

Discussion: People taking orlistat are advised to take a daily multivitamin preparation due to the possible reduction in uptake of fat-soluble vitamins. In addition, orlistat can reduce the absorption of amiodaron and cyclosporin. When taking oral anticoagulants, the coagulation parameters should be checked.

As sibutramin can increase blood pressure and heart rate, monitoring is recommended and its use is contraindicated for patients known to have cardiovascular complications. The simultaneous use of centrally working drugs for psychiatric illnesses, for weight loss or with tryptophan for sleeping disorders is contraindicated.

There is also a lack of experience in administering orlistat and sibutramin to children and the elderly, in cases of insufficiency of the liver and renal system and during pregnancy and lactation. Efficacy and safety data of orlistat will be available in four years' time. Sibutramin may only be used for one year; limited data are available on its use for longer than one year.

Conclusion: Some differences in the applicability of the weight-reducing drugs exist.

4.e. User-friendliness

Rimonabant and sibutramin are administered orally: 1 tablet/capsule in the morning before breakfast. Orlistat is taken in the form of a single capsule prior to, during or immediately after a meal (if the meal contains fat).

5. Other considerations

5.a. Costs

Table 4. Pharmacy purchase price (excl. VAT)

Drug	Price (€)	Dose (DDD)	Costs (€) per 28 days
Rimonabant	70 euros per 28 20-mg tablets	20 mg/day	70 euros
Orlistat	73.28 euros per 84 120-mg capsules	Three X 120 mg per day	73.28 euros
Sibutramin	23.63 euros per 28 15-mg capsules	15 mg/day	23.63 euros

5.b. Specific details

Rimonabant was also studied in the STRATUS-trials with regard to its role in ceasing smoking. The data were not unequivocal and the manufacturer has withdrawn the request for this indication.

6. Value of rimonabant as indicated by the manufacturer

6.a. *Manufacturer's claim*

The manufacturer indicates that rimonabant has a therapeutic added value for the entire registered field of indication in comparison with diet and exercise and in comparison with drugs with a weight-reducing effect. The manufacturer considers the greatest added value to be for two sub-populations with a considerable initial high risk of heart disease and vascular disease, whereby abdominal obesity plays an important role in the pathological process. These are patients with type 2 diabetes mellitus and genetically combined hyperlipidemia. In the current treatment of these two groups of patients, the emphasis is on regulating the glucose and/or lipid metabolism. In the opinion of the manufacturer, if patients do not benefit from this standard treatment, there is a medical necessity to deal with the abdominal obesity and the related risk factors, as well as to regulate the glucose and lipid metabolism. The considerable added value of rimonabant lies in the fact that it reduces and simultaneously regulates the abdominal HbA1c, HDL cholesterol, triglycerides and insulin-resistance.

6.b. *CFH's opinion on the manufacturer's claim*

Diet and physical exercise are the most important mainstays of treating excess weight and obesity. If these lead to insufficient results, then drugs may be able to play a role. The efficacy of these weight-reducing drugs is modest and demonstrates a plateau effect after a number of months. Apart from this, there are unwanted side effects. After termination, the weight loss is largely undone. Furthermore, there is no evidence that a stable weight loss of 5-10% reduced morbidity and mortality. Risk factors (e.g., increased cholesterol, HbA1c level) can be reduced. However, effective drugs are already available that have a favourable effect on the lipids and the glucose metabolism and which have been proven to reduce the risk of (new manifestations) of heart and vascular diseases.⁵

Statins are used for disorders in the lipid metabolism (hypercholesterolemia) and gemfibrozil (for combined hyperlipidemia). For the rest, treatment with a statin is advised for almost all type 2 diabetes mellitus patients, independent of the level of cholesterol. The effectiveness of these drugs on concrete endpoints has been demonstrated. No such data are available for rimonabant. A strict glycaemic adjustment is required for patients with diabetes mellitus. Monotherapy using metformin is first choice here. If results with maximum doses of metformin are insufficient, then a short-lasting sulphonylureum derivative is added. Effectiveness of these drugs on long-term complications, in particular microvascular ones, has been demonstrated. A reduction in the number of macrovascular complications has been demonstrated for metformin in a sub-group of patients with type 2 diabetes mellitus and overweight. In order to reduce the latter complications, treating the risk factors for heart and vascular diseases, such as hypertension and hypercholesterolemia, and in particular giving up smoking, is of greater importance.²¹ Rimonabant has not been studied as adjuvant in treating patients with type 2 diabetes mellitus with the maximum dose of oral blood-sugar-reducing drugs.

7. CFH-advice

7.a. Background

The Committee does not envisage a place for the weight-reducing drugs orlistat and sibutramin. When all's said and done, the weight loss achieved with orlistat is extremely limited (<5%). Sibutramin can only be used for one year, whilst terminating therapy leads to renewed weight gain.

7.b. CFH Advice

For the moment the Committee does not envisage a place for rimonabant in the treatment of obesity. In studies lasting 1-2 years rimonabant can lead to a limited extra weight loss (about 5%) when added to a moderately hypocaloric diet in combination with sufficient daily physical exercise. A number of risk factors associated with obesity can also improve; however, there is no evidence that this has a positive effect on morbidity and mortality.

8. Literature

¹ Zelissen PMJ, Matus-Vliegen EHM. Behandeling van overgewicht en obesity bij volwassenen: voorstel voor een richtlijn. Ned Tijdschr Geneeskd 2004;148(42): 2060-6.

² De diagnose metabool syndroom wordt meestal gesteld indien sprake is van drie of meer van de volgende criteria: abdominale obesity (middelomtrek mannen > 102 cm, vrouwen >88cm), hypertriglyceridemie (triglyceridengehalte >1,7 mmol/l), HDL cholesterolgehalte mannen <1,0 mmol/l, vrouwen <1,3 mmol/l, hypertensie (>130/85 mmHg), nuchter serumglucosegehalte > 6,1 mmol/l).

³ National Cholesterol Education Program (NCEP), Expert Panel on Detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.

⁴ Loenen AC. Farmacotherapeutisch Kompas 2007. Tractus ciruclatorius, pag. 281-3.

⁵ CBO. Multidisciplinaire richtlijn cardiovasculair risicomanagement. Alphen aan den Rijn : Van Zuiden Comm., 2006.

⁶ Kahn R, Buse J, Ferrannini E et al. The metabolic syndrome: time for a critical appraisal Joint Statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diab Care 2005;28:2289-304.

⁷ Gezondheidsraad. Overgewicht en obesity, Den Haag: Gezondheidsraad, 2003; publicatie nr 2003;publicatie nr 2003/07.

⁸ Williamson DF, Thompson TJ, Thun M et al. Intentional weight loss and mortality among overweight individuals with diabetes. Diab Care 2000;23:1499-1504.

⁹ Padwal RS, Majumdar SR. Drug treatments for obesity: orlistat, sibutramine and rimonabant. Lancet 2007;369:71-7.

¹⁰ Padwal R, Li SK, Lau DCW. Long-term pharmacotherapy for obesity and overweight (review). The Cochrane Database of Systematic Reviews 2003, Issue 4. Art. No. CD004094.pub2.

¹¹ Van Gaal LF, Rissanen AM, Scheen AJ et al for the RIO-Europe Study Group. 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.

¹² Despres JP, Golay A, Sjostrom I for the rimonabant in Obesity-Lipids Study Group. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. New Engl J Med 2005;353:2121-34.

¹³ Pi-Sunyer FX, Aronne LJ, Heshmati HM et al for the RIO- North America Study Group. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight of obese patients. JAMA 2006;295:761-75.

¹⁴ Scheen AJ, Finer N, Hollander P et al, RIO-Diabetes Study Group. Efficacy and tolerability of rimonabant in overweight of obese patients with type 2 diabetes. Lancet 2006;368:1160-72.

¹⁵ Aanhangel 1b rimonabant

¹⁶ EPAR rimonabant

²¹ NHG-standaard Diabetes mellitus type 2 (tweede herziening). Huisarts Wet 2006;49:137-52.

This text was approved during the meeting of the Medicinal Products Reimbursement Committee on 26 February 2007.

The data from this pharmacotherapeutic report will be incorporated into section 19/d/10 of the Farmacotherapeutisch Kompas.