SINGLE TECHNOLOGY APPRAISAL

RIMONABANT FOR THE TREATMENT OF OVERWEIGHT AND OBESE PATIENTS

THE EVIDENCE REVIEW GROUP'S REPORT

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CRD, a research unit of the University of York, was established in January 1994, and is now the largest group in the world engaged exclusively in evidence synthesis in the health field. The centre undertakes high quality systematic reviews that evaluate the effects of health and social care interventions and the delivery and organisation of health care.

CHE is a research unit of the University of York. The Centre's aim is to undertake high quality research that is capable of influencing health policy decisions. The largest programme of work at CHE is that on economic evaluation and health technology assessment which focuses on a range of methodological and applied work. This includes full technology assessment reviews and evidence review reports for the National Institute for Health and Clinical Excellence (NICE).

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Conflicts of interest:

Mark Sculpher has been a consultant to Sanofi-Aventis and Roche but in areas unrelated to obesity and or the products covered in this STA. The remaining authors of this report have no conflicts of interest.

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BMI	Body mass index
BP	Blood pressure
CB-1	Cannabinoid type 1
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DES	Discrete events simulation
EMEA	European Medicines Agency
FDA	Food and Drugs Administration
FHS	Framingham Heart Study
FPG	Fasting plasma glucose
HbA_{1c}	Glycosylated haemoglobin
HDL-C	High-density lipoproteins-cholesterol
HoDAR	Health Outcomes Data Repository
HOMA-IR	Homeostasis model assessment for insulin resistance
HRQoL	Health related quality of life
hsCRP	High sensitivity C-reactive protein
ICER	Incremental cost effectiveness ratio
IHD	Ischaemic heart disease
ITT	Intention to treat
IWQOL-Lite	Impact Of Weight On Quality Of Life-Lite Questionnaire
LDL-C	Low-density lipoproteins- cholesterol
LOCF	Last observation carried forward
MI	Myocardial infarction

PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RIO	Rimonabant in obesity
RR	Relative risk
SBP	Systolic blood pressure
SD	Standard deviation
SF-36	Medical Outcomes Study Short Form 36
TC	Total (plasma) cholesterol
TEAEs	Treatment emergent adverse events
TG	Triglyceride
TIA	Transient ischaemic attack
tid	Three times daily
UKPDS	UK Prospective Diabetes Study
WMD	Weighted mean difference

1 SUMMARY

This document critically evaluates the evidence submission from Sanofi-Aventis (the manufacturer) on the clinical and cost-effectiveness of rimonabant (Accomplia®) as an adjunct to diet and exercise for the treatment of obese patients (BMI≥30kg/m^2), or overweight patients (BMI>27kg/m^2) with associated risk factors(s) such as type 2 diabetes or dislipidaemia. This report identifies the submission's strengths and weaknesses, supplemented, where appropriate, with the Evidence Review Group's (ERG) analysis. A clinical expert was asked to advise the ERG to help inform the review.

1.1 Scope of the submission

The submission from the manufacturer evaluates the evidence for the clinical-effectiveness, safety, tolerability and cost-effectiveness of rimonabant in its licensed indication as an adjunct to diet and exercise, relative to other licensed anti-obesity drugs (orlistat and sibutramine) and diet and exercise alone.

1.2 Summary of submitted clinical effectiveness evidence

1.2.1 Effectiveness of rimonabant

The evaluation of the efficacy of rimonabant focused primarily on the results of four Sanofi-Aventis sponsored RCTs (RIO-Europe,[1] RIO-North America,[2] RIO-Diabetes[3] and RIO-Lipids[4]). Two further trials were cited but did not contribute to the main meta-analyses (SERENADE[5] and REBA[6]). Data from two unpublished studies were used to inform the analysis of adverse effects (EFC5745 and ACT3801).

Rimonabant resulted in a significantly greater benefit than placebo in terms of all primary weight loss outcomes:

- Change in weight (kg): Non-diabetics: Weighted mean difference (WMD) -4.91 (95% CI: -5.35, -4.48); Diabetics: WMD -3.90 (95% CI: -4.57, -3.23)
- Proportion of patients losing 5% body weight: Non-diabetics: RR 2.61 (95% CI: 2.32, 2.95); Diabetics: RR 3.41 (95% CI: 2.58, 4.50)

- Proportion of patients losing 10% body weight: Non-diabetics: RR 3.48 (95% CI: 2.84, 4.27); Diabetics: RR 8.07 (95% CI: 3.37, 17.46)
- Change in waist circumference (cm): Non-diabetics: WMD -4.01 (95% CI: -4.50, -3.53); Diabetics: WMD -3.30 (95% CI: -4.17, -2.43)
- BMI (kg/m^2): Non-diabetics: WMD -1.76 (95% CI: -1.92, -1.60); Diabetics: WMD -3.90 (95% CI: -4.57, -3.23). For any baseline BMI, the average weight loss beyond that which can be achieved with diet and exercise over a one year period is around 5 kg with a fall in BMI of 1.7 kg/m^2.

At one year, rimonabant had a statistically significant beneficial effect on systolic blood pressure (SBP), HDL-cholesterol, triglycerides and fasting plasma glucose in both diabetic and non-diabetic patients, and HbA_{1c} in diabetic patients.

Two of the RIO trials reported significantly greater reductions in body weight in patients achieving 5% weight loss with rimonabant (RIO-North America; RIO-Lipids). None of the trials reported significantly greater reductions in body weight in patients achieving 10% weight loss with rimonabant, or in waist circumference in patients achieving 5% or 10% weight loss with rimonabant.

Weight loss and improvements in associated cardiovascular and diabetes risk factors are maintained over 2 years when rimonabant is continued, however, the relative benefit over placebo was lower in year 2. Following withdrawal of rimonabant treatment at 1 year, there was a gradual reduction in the rate of weight loss until there was no difference from placebo at two years.

Thirteen adverse events were identified by the manufacturer as being associated with rimonabant at a rate of ≥2%, and at a rate of ≥1% greater than placebo. These were nausea; diarrhoea; vomiting; dizziness; anxiety; insomnia; mood alterations with depressive symptoms; depressive disorders; influenza; asthenia/fatigue; gastroenteritis; contusion, and hot flushes.

Two separate instruments were used to evaluate the effect of rimonabant on health related quality of life (HRQoL). One was the obesity specific Impact of

Weight on Quality of Life-Lite (IWQOL-Lite) and the other the generic Medical Outcomes Study Short Form 36 (SF-36). Rimonabant provided benefits in some areas of HRQoL, particularly physical functioning, but was associated with a significant deterioration in mental health.

1.2.2 Comparison of rimonabant with orlistat and sibutramine

In the absence of head-to-head trials, the manufacturer provided tabulated comparisons between the placebo-subtracted results for orlistat, sibutramine and rimonabant. On request, pairwise comparisons between rimonabant and sibutramine and orlistat were provided for the primary outcomes. These pairwise comparisons showed significant increase in the number of patients achieving 5% weight loss with rimonabant compared to sibutramine in the non-diabetic population (RR 1.30; 95% CI: 1.14; 1.48). In addition, rimonabant compared favourably with orlistat:

- Body weight: Non-diabetics: WMD -2.10 (95% CI: -2.62, -1.58); Diabetics: WMD -1.37 (95% CI: -2.17, -0.57); Dyslipidaemics: WMD -1.90 (95% CI: -2.96, -0.84)
- Waist circumference: Non-diabetics: WMD -2.52 (95% CI: -3.10, -1.94); Dyslipidaemics: WMD -3.20 (95% CI: -4.85, -1.55)
- Change in BMI: Non-diabetics: WMD -0.83 (95% CI: -1.45, -0.21)
- Patients who achieved 5% weight loss: Non-diabetics: RR 1.62 (95% CI: 1.51; 1.75); Diabetics: RR 1.72 (95% CI: 1.27; 2.33)
- Patients who achieved 10% weight loss: Non-diabetics: RR 1.83 (95% CI: 1.47; 2.27); Diabetics: RR 3.67 (95% CI: 1.62; 8.33).

There was no comparison of adverse events or HRQoL between rimonabant and orlistat or sibutramine.

1.3 Summary of submitted cost effectiveness evidence

Only one previously published study reporting on the cost-effectiveness of rimonabant was identified. This study evaluated the cost-effectiveness of rimonabant compared to diet and exercise alone. No published studies were

identified that had compared rimonabant with other licensed anti-obesity drugs.

The manufacturer's submission was based on a *de-novo* economic evaluation of rimonabant compared to orlistat, sibutramine and diet and exercise alone. Separate models were presented based on a Markov cohort model and a patient-level approach using discrete event simulation. The main submission focused on the Markov cohort model.

The Markov model evaluated the following treatment comparisons: (i) lifetime rimonabant plus diet and exercise versus lifetime diet and exercise alone; (ii) lifetime rimonabant plus diet and exercise versus lifetime orlistat plus diet and exercise; and (iii) 1 year rimonabant plus diet and exercise versus 1 year sibutramine plus diet and exercise. The results of the economic evaluation were presented for 3 base-case populations, comprising: (i) overweight or obese patients with treated type 2 diabetes (diabetic group); overweight or obese patients with dyslipidaemia not treated with a statin, and without type 2 diabetes (dyslipidaemic group) and (iii) obese patients with or without comorbidities (obese group). A number of additional subgroups were considered as part of the sensitivity analysis.

In the absence of direct head-to-head RCT data for the alternative strategies, indirect approaches were employed to assess the relative effectiveness of each treatment strategy in terms of their impact on a number of established risk factors for cardiovascular disease (CVD) and diabetes. A series of published risk equations was used to translate changes in these risk factors to a reduced risk of CVD and, in patients without diabetes, to a reduced risk of developing diabetes. The effect of the treatments on BMI was also assumed independently to influence HRQoL beyond that attributed to the effect on CVD and diabetes risks. These approaches were used as the basis for estimating quality-adjusted life years (QALYs) over a lifetime time horizon. Costs were based on the drug acquisition and monitoring costs, adverse events and the costs of CVD and diabetes. Costs and QALYs were compared and incremental cost-effectiveness ratios (ICERs) of rimonabant estimated where

appropriate. The robustness of the results was assessed using deterministic and probabilistic sensitivity analyses.

Across the base case populations, the ICER of rimonabant varied between £10,534 to £13,236 per QALY (versus diet and exercise), £8,977 to £12,138 per QALY (versus orlisat) and £1,463 to £3,908 per QALY (versus sibutramine). In the additional subgroups considered there was a wider variation in the ICER estimates; however, none of the individual pairwise ICERs for rimonabant exceeded £20,000 per QALY in any of the subgroups. The ICER estimates across the majority of the sensitivity analyses were broadly consistent with the base-case results.

The ERG considered that the original submission contained a number of important uncertainties and issues which potentially compromised the validity of the model results. A number of these issues were addressed by the manufacturer as part of their response to the ERG's points for clarification. The ERG identified a number of remaining issues related to the manufacturer's response and several of these were subsequently addressed with additional analyses conducted by the ERG. The ICER of rimonabant remained relatively robust throughout the re-analyses by the manufacturer and the ERG (<£20,000 per QALY), although the results did appear to be sensitive to the source of HRQoL benefits assumed in the model, with markedly less favourable ICER estimates using data from the RIO trials. However, the ERG considered that several important caveats and uncertainties remained.

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

The manufacturer's submission presents a clear overview of the four major trials (RIO trials) conducted with rimonabant in overweight or obese patients with data for up to two years. The submission also included a comparison with the appropriate comparators orlisat and sibutramine.

The manufacturer used appropriate criteria to assess the quality of the RIO trials, although ERG noted some discrepancies between the assessments provided in the submission and those information available in published trial reports. The ERG assumes that the manufacturer had access to the full trial reports.

The manufacturer's submission was considered to comprise the most relevant source of cost-effectiveness evidence related to the use of rimonabant. The ERG identified a number of strengths in the manufacturer's cost-effectiveness analysis. The overall model structure, approaches to estimating long term costs and outcomes (expressed using QALYs), the time-horizon employed and the approach to handling parameter uncertainty were all consistent with the NICE Reference Case for cost-effectiveness analysis. The ERG also noted that the manufacturer had compared rimonabant against other licensed anti-obesity drugs as well as diet and exercise alone. A broad range of sensitivity analyses was also undertaken to explore alternative assumptions. Variation in the cost-effectiveness estimates for rimonabant was considered in a number of different patient subgroups. The ERG also felt that the validation approaches employed by the company (including presenting the results of a separate discrete-event simulation) were a relative strength of the submission. Finally, the ERG felt that the manufacturer had attempted to address a number of areas of uncertainty identified by the ERG in their response to the points for clarification.

1.4.2 Weaknesses

The four included trials may not be generalisable to the UK population, both in terms of the baseline BMIs and the differences in lifestyle, diet and attitudes towards alcohol consumption and exercise, between the UK, and the USA and other European countries. Furthermore the diabetic patients included in the manufacturer's submission did not include insulin dependant diabetics and so may not be generalisable to the broader diabetic population.

The comparison of the effects of rimonabant on weight loss outcomes with those of orlistat and sibutramine is uncertain given the differences in diet and

exercise that might have been employed across the different trials. There was no comparison of 2 year data between rimonabant and orlistat. There are differences in the licence of rimonabant compared to orlistat and sibutramine; orlistat and sibutramine are subject to response hurdles in practice that may not be applied in trials, therefore any additional benefit of rimonabant over orlistat or sibutramine may be overestimated, and not be apparent in normal clinical practice.

Overall, the ERG found the presentation of the data unclear, particularly that for orlistat and sibutramine. The ERG has concerns over how representative of the general literature the trials of orlistat and sibutramine in the submission are, and how objectively the data have been used.

The ERG identified a number of potential weaknesses in the manufacturer's cost-effectiveness analysis. The most significant was considered to be the lack of response 'hurdles' applied to sibutramine and orlisat, such that the comparator strategies were not considered by the ERG to reflect their respective product licences or current NHS use. While this issue was partially addressed by the manufacturer in their response to the ERG points for clarification, the ERG did not consider that this aspect had been robustly considered by the manufacturer and hence represents a major limitation. The ERG also considered the manufacturer's approach to evaluating HRQoL benefits to be subject to a number of important uncertainties. The ERG considered that the manufacturer's reliance on external utility estimates, as opposed to the HRQoL data reported in the RIO trials, was a potential weakness. Indeed, the HRQoL benefits associated with rimonabant remain highly uncertain and need more detailed investigation by the manufacturer.

1.4.3 Areas of uncertainty

Areas of uncertainty remain in relation to the clinical effectiveness and safety of rimonabant. A major area where data is lacking relates to the long-term outcomes, with no effectiveness or safety data presented for rimonabant beyond 2 years, and available data beyond 1 year limited. Also, the manufacturer has identified no direct evidence for the effect of rimonabant on

hard clinical endpoints, such as cardiovascular events, developing diabetes, and mortality. The manufacturer state that results from an ongoing trial, CRESCENDO, which is evaluating the effect of rimonabant on cardiovascular morbidity and mortality, are expected to be available in 2011.

Given that lack of head-to-head comparisons between rimonabant and orlistat or sibutramine with all three drugs given as per licence, it is unclear whether the pairwise comparisons between rimonabant and orlistat and sibutramine presented in the clarification submission, will reflect that seen in clinical practice; response hurdles imposed on orlistat or sibutramine in clinical practice may not have been applied in the orlistat and sibutramine trails.

With respect to cost-effectiveness, a number of issues and uncertainties were addressed by the manufacturer in their response to the ERG's points for clarification. Some remaining issues relating to the manufacturer's response were subsequently addressed with additional analyses conducted by the ERG. However, some caveats and uncertainties remain. Firstly, the lack of response hurdles applied to orlistat and sibutramine in the modelling. Although this has partially been addressed in the manufacturer's response subsequent to the initial submission, the ERG feels that this has not resolved the uncertainties in this area. Secondly, the way HRQoL was handled in the modelling. The use of, and selection of, evidence relating BMI to utility from outside the main trials is an important source of uncertainty.

1.5 Key issues

- The adequacy of the cost-effectiveness modelling and assumptions regarding strategies utilising response hurdles for rimonabant and comparator treatments is a key concern.
- The use of external evidence on the HRQoL impact of BMI independent of longer-term clinical events rather than estimates from the trials. Furthermore, the choice of this external evidence is a key issue.
- The lack of evidence linking the effect of rimonabant on 'hard' endpoints, such as CVD, diabetes and mortality.

- There is a lack of data for the effectiveness and safety of rimonabant beyond 2 years.
- The appropriateness of incorporating the link between BMI reductions and a lower risk of diabetes and CVD and the choice of evidence to inform this link.
- There are concerns over the psychiatric morbidity associated with rimonabant, and given this lack of long-term data, the cumulative data on less common side-effects is uncertain.
- Generalisability to the UK overweight and obese population is uncertain, particularly in the broader diabetic population as there are no data for the effectiveness or safety of rimonabant in insulin dependant diabetics.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The manufacturer's submission adequately, if briefly, described the aetiology and epidemiology of overweight and obesity. The rationale for the development of rimonabant and its mechanism of action as a selective antagonist of cannabinoid type 1 (CB-1) receptor within the central nervous system is also briefly outlined. The description of the epidemiology and the general management of overweight and obese patients in current practice draws heavily on existing NICE guidance.[7]

2.2 Critique of manufacturer's overview of current service provision

The manufacturer's submission states that since the introduction of rimonabant, until the end of June 2007, approximately 32,500 patients have been prescribed rimonabant in England and Wales, accounting for 16.4% of prescription initiations for obesity treatments during that period. Prescription surveys by the manufacturer showed that approximately 87% of prescriptions were in patients with a BMI >27 kg/m^2 with risk factors, and 12% in patients with BMI ≥ 30 kg/m^2 without risk factors. For patients with comorbidities, which accounted for a large majority of rimonabant prescriptions, the

manufacturer did not indicate the proportion of patients belonging to each BMI category, nor categorise by risk group. The manufacturer did state that the average BMI is approximately 37 kg/m^2, average age approximately 47 years, and that prescriptions were distributed equally between men and women. No breakdown of the statistics for the use of orlistat or sibutramine was provided.

More detail could have usefully been provided about the benefits and limitations of current treatment options. There was no background information relating to the use, effectiveness or safety of orlistat or sibutramine, the two active comparators for rimonabant that are used in clinical practice. There was also no summary of the efficacy of, or compliance with, dietary and exercise regimes.

There are currently several options for the treatment of overweight and obesity. These include: lifestyle changes; drug treatment; and bariatric surgery. Multicomponent interventions that include behavioural change strategies to increase people's physical activity levels or decrease inactivity, improve eating behaviour and the quality of the person's diet and reduce energy intake are, according to the NICE guidelines, the initial treatment of choice for overweight and obese patients.[7]

Current NICE guidelines indicate that the decision to initiate drug treatment, and the drug chosen, should be made after discussing with the patient potential benefits and limitations (including the mode of action, adverse effects and monitoring requirements and their potential impact on the patient's motivation). If drug treatment is prescribed, information, support and counselling on additional diet, physical activity and behavioural strategies should be provided by appropriate health professionals and information on patient support programmes provided. [7]

Bariatric surgery is recommended by NICE as a first-line option for adults with a BMI >50 kg/m^2 in whom surgical intervention is considered appropriate. [7] As bariatric surgery is recommended in this restricted population, it is not an

appropriate comparison for rimonabant and was not considered in the manufacturer's submission.

When considering drug treatments (the focus of the submission) three drugs are currently used in practice; orlistat (Xenical®, ROCHE), sibutramine (Reductil®, Abbott) and rimonabant (Accomplia®):

- Orlistat is a specific and long-acting inhibitor of the enzyme lipase, which results in the inability to hydrolyse dietary fat in the form of triglycerides, into absorbable free fatty acids and monoglycerides, therefore preventing fat absorbtion.[8] The net price per 84-cap pack is £33.58. with an approximate annual cost of £438.[9]
- Sibutramine produces secondary and primary amine metabolites which inhibit noradrenaline, serotonin and dopamine reuptake, which in turn suppresses appetite by producing a feeling of satiety.[8] The net price per 28-cap pack of 10 mg is £36.90. The net price per 28-cap pack of 15 mg is £43.65. The approximate annual cost is £481 for 10mg and £569 for 15mg.[9]
- Rimonabant is a selective CB1 cannabinoid receptor antagonist and acts by decreasing appetite.[10] The net price per 28-tab pack is £44.00, with an approximate annual cost of £574.[9]

The licences and guidance for the use for these drugs are outlined in Section 3.3.

Concerns have been raised relating to the licensing of rimonabant, both in the UK and the USA. In January 2007, the Scottish Medicines Consortium did not recommend rimonabant for use within NHS Scotland as an adjunct to diet and exercise for the treatment of obese patients (BMI $\geq$30 kg/m^2), or overweight patients (BMI >27 kg/m^2) with an associated risk factor or risk factors such as type 2 diabetes or dyslipidaemia.[11] They stated that although rimonabant was associated with a reduction in mean weight of about 4-5kg over placebo, weight was generally regained within one year of stopping treatment, and that the economic case had not been demonstrated. The Food and Drugs Administration (FDA) also did not recommend a licence for rimonabant in the USA, due to the risk of psychiatric adverse events, particularly the incidence

of suicidality and suicidal ideation, associated with rimonabant.[12] The safety profile of rimonabant was reviewed by the European Medicines Agency (EMEA),[13] and now precludes the use of rimonabant in patients with ongoing major depressive illness and/or ongoing antidepressive treatment.[14]

3 Critique of manufacturer's definition of decision problem

3.1 Population

The population was defined as adults who were obese (BMI $\geq$30 kg/m^2) or who were overweight (BMI >27 kg/m^2) with comorbidities (e.g. diabetes or dyslipidaemia), reflecting the UK product licence for rimonabant.

3.2 Intervention

The intervention evaluated was the licensed dose of rimonabant, 20mg once daily, in conjunction with diet and exercise. Reflecting the product licence, there were no specific inclusion criteria relating to the type or degree of diet and exercise to be undertaken as an adjunct to rimonabant.

3.3 Comparators

Three comparators to rimonabant were considered in the manufacturer's submission: placebo; orlistat; and sibutramine, all in conjunction with diet and exercise. Given that these are the alternative interventions utilised in clinical practice, they are appropriate comparators for the evaluation of rimonabant. There were no specific inclusion criteria relating to the type or degree of diet and exercise to be undertaken as an adjunct to placebo.

Orlistat [7, 8]:

Orlistat 120 mg three times daily Indicated in conjunction with a mildly hypocaloric diet for patients with:

- A body mass index (BMI) of 28 kg/m^2 or more and have another serious illness which persists despite standard treatment. (E.g. Type 2 diabetes, high blood pressure and/or high cholesterol).

or

- A BMI of 30 kg/m^2 or more with no associated illnesses

Treatment with orlistat should be discontinued after 12 weeks if patients have been unable to lose at least 5 % of the body weight as measured at the start of drug therapy.

Sibutramine [7, 8]:
Sibutramine 10 or 15 mg taken once daily is indicated as adjunctive therapy within a weight management programme in patients who have not adequately responded to an appropriate weight-reducing regimen alone, and who:

- Have nutritional obesity and a body mass index (BMI) of 30 kg/m^2 or higher

or

- Have nutritional excess weight and a BMI of 27 kg/m^2 or higher, if other obesity-related risk factors such as type 2 diabetes or dyslipidaemia are present.

Treatment with sibutramine 10 mg / 15 mg should only be given as part of a long-term integrated therapeutic approach for weight reduction under the care of a physician experienced in the treatment of obesity, such as dietary and behavioural modification and increased physical activity.

People taking sibutramine must discontinue treatment if:

- Patients have not lost 2 kg in weight within 4 weeks
- Patients have not lost at least 5% of their body weight after 3 months of treatment
- Patients regain 3 kg or more after previously achieved weight loss

In patients with associated co-morbid conditions, it is recommended that treatment with sibutramine should only be continued if it can be shown that the weight loss induced is associated with other clinical benefits, such as improvements in lipid profile in patients with dyslipidaemia or glycaemic control of type 2 diabetes.

Because sibutramine can lead to increases in blood pressure, people taking it should have their blood pressure checked regularly. Increases in blood pressure should be considered carefully, and may be a reason to stop treatment. Sibutramine is not recommended for patients who already have high blood pressure (145/90 or above).

Sibutramine should not be prescribed for periods over one year.

Rimonabant[7, 8]

Rimonabant 20 mg once daily as an adjunct to diet and exercise for the treatment of:

- Obese patients (BMI ≥30 kg/m^2),

or

- Overweight patients (BMI >27 kg/m^2) with associated risk factor(s) such as type 2 diabetes or dyslipidaemia.

As can be seen both orlistat and sibutramine are subject to response hurdles if patients have not achieved the expected degree of weight loss. Rimonabant on the other hand, is not subjected to such restrictions in its licence. The clinical advisor to the ERG stated that it is unclear why there were no definite response hurdles in the licence for rimonabant, and there seemed to be no reason why reasonable weight loss (at least 5%) should not be expected at 3 months. In clinical practice, prescription of the drug would be unlikely continue if no benefit was evident at this time (except perhaps in selected refractory patients in primary care), and the apparent 9 month lag in achieving optimal weight loss with rimonabant (as considered by the manufacturer) may be linked to 'stages of change' (psychological readiness for weight management programme) rather than any pharmacological effect. This view was supported by the evidence statements submitted by clinicians (Association of Clinical Diabetologists and the Royal College of Physicians) who stated that it is not logical to continue treatment if the patient hasn't shown any response by 3 months, and prescription should be withdrawn if a patient has not achieved at least a 5% weight loss by this time.

The issue surrounding response hurdles has an impact on the choice of active comparator, and the applicability of the comparisons to clinical practice. The most appropriate comparison between rimonabant and either orlistat or sibutramine would be as per licence for each drug. Therefore, if the response hurdles applied to orlistat and sibutramine in practice, are not applied in trials evaluating these drugs, the outcomes at 1 year would include non-responders who would otherwise have discontinued treatment in practice. This therefore, could lead to an underestimation of the effectiveness of these drugs in trials when compared to clinical practice. Therefore, if results from trials of rimonabant, where use is as per licence (without response hurdles), are compared to results from trials of orlistat or sibutramine without response hurdles, any additional benefit of rimonabant over orlistat or sibutramine may be an overestimation of what can be achieved in clinical practice. The failure to include a comparison where all relevant response hurdles are applied to all drugs means that not all relevant comparators will have been considered.

3.4 Outcomes

The outcomes considered in the manufacturer's submission were weight associated measures (body weight and BMI change from baseline at 1 and 2 years, proportion of patients achieving 5% or 10% weight loss, change in waist circumference), safety and tolerability (adverse events, withdrawal due to adverse events), quality of life (IWQOL, SF-36), diabetic and cardiovascular risk factors (cholesterol levels, triglycerides, glycaemic control, blood pressure) and mortality. Data on cardiovascular events, diabetic events and mortality were not available in the publications of the RIO trials, and no data were presented for these outcomes in the manufacturer's submission. Given the response hurdles imposed on the two active comparators as outlined above, the lack of outcome data at three months for rimonabant precludes an assessment by the ERG of a scenario for rimonabant comparable to that of orlistat and sibutramine in clinical practice.

3.5 Time frame

Currently, evidence is available for up to 2 years. However, there is a high rate of drop outs from the trials for which these data are available. The manufacturer only provides outcome data for rimonabant at 1 year and 2 years. Given the lack of data beyond 2 years, and the limited data available beyond 1 year, the effectiveness and safety of rimonabant in the longer term remains uncertain.

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

4.1.1 Description of manufacturers search strategy and comment on whether the search strategy was appropriate.

The submission reports a search of most of the required databases for records of reviews and randomized controlled trials relating to effects of rimonabant, sibutramine and orlistat. NICE requires a search of the Cochrane Library, but the submission reports only a search of the Cochrane Database of Systematic Reviews. This may mean that the CENTRAL Register of Clinical Trials, DARE and the HTA database were not searched. The submission reports that an additional relevant database, Biosis, was searched.

A MEDLINE search strategy only is reported. The database searches were reported to have been run on Datastarweb, but the search syntax (truncation symbols etc.) reported is not correct for Datastarweb. The ERG was unable to rerun the strategy, as presented, in the PubMed, Datastarweb or Ovid interfaces to MEDLINE. The ERG was also unable to verify how the strategy was adapted for databases other than MEDLINE. However, the structure of the search strategy as reported is suitable for capturing the topic in MEDLINE.

The words used in the strategies for identifying evidence on the effects of rimonabant, sibutramine and orlistat are adequate to capture the topic. One search term reported is not a MeSH term (HYPERLIPIDAEMIA). The relevant MeSH terms for the topics in this section of the strategy should be DISLIPIDEMIAS/, HYPERLIPIDEMIAS/ and HYPERCHOLESTEROLEMIA/.

Although the use of these terms was not reported, the presence of a variety of textwords describing dyslipidaemia and hyperlipidaemia within the strategy should compensate for the omission, as long as those textwords were being searched in all text fields.

Some MeSH Publication Types included in the strategy are no longer search options: REVIEW TUTORIAL, REVIEW OF REPORTED CASES, REVIEW MULTICASE. However, this does not affect the sensitivity of the search. The set combination in line 18 to reduce the retrieval of records about diabetes insipidus runs the risk of also removing possibly relevant records about type 1 and type 2 diabetes. The use of an approach similar to the animal exclusion in line 27 might have been safer. In some sections of the strategy there are harmless redundant search terms (for example, dependent on the search interface, searching on ‘diabet’ obviates the need for searches on more specific terms such as ‘type 1 diabetes’).

In the search strategy used to retrieve evidence on orlistat and sibutramine, some of the weight loss terms used in the rimonabant search do not appear (see line 22). If this reflects the search that was undertaken, the sensitivity of the search for orlistat and sibutramine may have been lower than for rimonabant.

The submission records that reference lists of retrieved papers were reviewed to identify additional articles. This is accepted practice.

The manufacturer identified data from unpublished trials presented at conferences from its own files only: “unpublished data held on file by Sanofi-Aventis” (p.21). Data from SERENADE and REBA trials are included in the submission (p.21). Searches of other external resources for trial information in the form of presentations, abstracts and posters were not reported to have been undertaken. In response to a request for clarification, the manufacturer stated that they did not search for data from ongoing (soon to report) studies.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

For the review of rimonabant compared with placebo, the selection criteria were as stated in the decision problem. However, when selecting studies for the review, the manufacturer broadened the criteria for population from obese adults (BMI $\geq$30 kg/m^2), or overweight adults (BMI >27 kg/m^2) with comorbidities, to include people with a BMI >25 kg/m^2 with a comorbid condition. The manufacturer states that this was in order that studies that had recruited what may have been a small proportion of patients at this lower BMI level were not automatically excluded, maximising the available data.

The manufacturer identified three base-case populations:

- Overweight or obese patients with treated type 2 diabetes
- Overweight or obese patients with dyslipidaemia (defined as triglycerides > 1.7 mmol/L or total plasma cholesterol > 5.0 mmol/L or LDL-C > 3.0 mmol/L or HDL-C <1.03 mmol/L for men, and triglycerides > 1.7 mmol/L or total plasma cholesterol > 5.0 mmol/L or LDL-C > 3.0 mmol/L or HDL-C <1.29 mmol/L for females) not treated with a statin, and without type 2 diabetes
- Overweight and/or obese patients with or without comorbidities, without diabetes.

These groups seem to reflect the RIO trials rather than subgroups of importance in clinical practice. A notable omission is a subgroup of patients with hypertension. The applicability of these base-case populations to clinical practice are discussed in Section 5.2.2.

For the review of orlistat and sibutramine the inclusion criteria were:

- Studies of 1 year duration (or data available for 1 year).
- Diet and exercise administered to placebo and treatment arms.
- Data for ITT population available (if this was not stated, it was assumed that data presented in the studies were for the ITT population and they were not excluded).

- Orlistat dose of 120 mg tid or 120 mg with each meal.
- Sibutramine dose of 10 or 15 mg/day.
- Data relating to trial run-in periods (if applicable) were excluded from the analysis.

In addition, the inclusion of studies in the meta-analyses undertaken by the manufacturer was dictated by the base-case analyses specified, which in turn reflect the characteristics of the main trials of rimonabant.

The inclusion criteria for the doses of orlistat and sibutramine appear clinically appropriate. All the trials evaluating orlistat included the dose of 120 mg three times daily as specified in the inclusion criteria; several trials also evaluated 30 mg or 60 mg three times daily. Two of the included sibutramine trials did not appear to meet the inclusion criteria; these two trials evaluated 20 mg of sibutramine once daily. Data for orlistat and sibutramine were only sought for 1 year; although this is appropriate for sibutramine given its licence (see Section 3.3), orlistat can be prescribed for longer, and two year data may have been available for comparison with the longer-term outcomes reported in the RIO trials.

The submission states that studies were screened by a single reviewer at both the title/abstract stage and the full paper stage, with a second reviewer screening only approximately 10% of identified studies. This could lead to missed studies and selection bias, particularly when considering the orlistat and sibutramine trials as it seems that some of the reasons for exclusion could be deemed subjective and judgements may vary between reviewers. In addition, no description is provided of methods for resolving disagreements where dual screening was undertaken.

Overall, the ERG has concerns about how representative of the general literature the trials of orlistat and sibutramine included in the submission are, and how the objectively the data have been used. The ERG have therefore

compared the results for orlistat and sibutramine included in the submission with those presented in the NICE guidelines (see Section 4.3.4.1).[7]

4.1.3 Table of identified studies. What studies were included in the submission and what were excluded.

Regarding the efficacy of rimonabant, the submission focused primarily on the results of four Sanofi-Aventis sponsored RCTs (RIO-Europe,[1] RIO-North America,[2] RIO-Diabetes[3] and RIO-Lipids[4]). Two further trials that the manufacturer stated were ongoing were cited in the review as supporting reported findings (SERENADE[5] and REBA[6]) but were not reported in detail in the manufacturer's original submission, and did not contribute to the main meta-analyses. Justification was given for not pooling data from the SERENADE trial with that from the RIO-Diabetes trial in the meta-analyses, namely that the trial was of a shorter duration than the RIO-Diabetes trial. The manufacturer states that results from the SERENADE trial support those of the RIO trials, but at no point provides the data to support this.

Data from two further studies from the company's obesity programme of studies have been used to inform some analysis of adverse effects (EFC5745 and ACT3801). These studies were not identified as passing the inclusion criteria, and no information or citations were provided in the initial submission in support of their use. On request by the ERG, further information on these two trials was provided, and were identified as recently completed in-house, unpublished, trials. The trial EFC5745 was of 3 months duration and an investigation of the effect of rimonabant on insulin sensitivity, and ACT3801was of 6 months duration and was a trial investigating the effect of rimonabant of binge eating in obese patients. The REBA trial is primarily a study of the effects of rimonabant on energy intake (Table 4.2).[6]

The REBA, EFC5745 and ACT3801 trials are used only to inform the adverse events data, although SERENADE is not. As it would be expected that a number of adverse events become evident soon after commencing rimonabant, it seems appropriate that these shorter-term trials are used to inform on adverse events, even if it was considered inappropriate that they

inform on efficacy. However, clinical advice to the ERG has stated that the cumulative data on less common side-effects over the longer-term is potentially important.

Regarding the reviews of orlistat and sibutramine, the ERG has been unable to verify that the included studies, and the data used from them, comprise the body of evidence against which rimonabant should be compared. Of particular concern is the subjective selection of trials to those matching the base-case populations and subgroups reported in the RIO trials. Furthermore, the number of studies included in many 'pooled' analyses is often small (sometimes only a single study),), without being made explicitly clear in the submission.

Of particular concern is the question of which studies were used to derive data for the non-diabetic group; it appears that the data for orlistat and sibutramine reported in Tables 21 and 22 are derived from different populations. The data for orlistat are derived from all obese patients, with or without dyslipidaemia but without diabetes (base-case 3b); data for sibutramine are derived from all obese and overweight patients with dyslipidaemia (sensitivity analysis 1).

The manufacturer excluded a trial that evaluated orlistat that met the inclusion criteria.[15] This subjective selection of studies may have introduced bias.

Table 4.1: Details available from the published reports of the included trials of rimonabant, as extracted by the ERG; data from the EFC5745 and ACT3801 trials have not yet been published.

Description	Quality	Outcomes (ITT; LOCF) Change from baseline (SD)
Rio-Diabetes[3] n=1045; n=692 at 1 year follow-up BMI 27-40 kg/m^2 adults with Type 2 diabetes (>18 years) 5mg/day or 20mg/day rimonabant vs placebo Mean age: Placebo: 54.8 (SD: 8.6); 20mg rimonabant: 56.0 (SD: 8.5) Number male: Placebo: 159 (46%); 20mg rimonabant: 168 (50%) Mean BMI: Placebo: 34.2 (SD: 3.6); 20mg rimonabant: 34.1 (SD: 3.6) 4 week placebo run in period	**Randomisation**: Centrally generated randomised code list; blocks of 3; 1:1:1 ratio. **Allocation concealment**: Interactive voice response system **Blinding**: Double blind **Sample size calculation**: Yes **Withdrawals/dropouts**: Completed by: Placebo: 66%; 20mg rimonabant: 68% **Analysis**: ITT of all patients who received at least 1 dose of their allocated placebo/treatment drug and had at least one post-baseline assessment, or in some cases (where authors say is appropriate) just a baseline assessment. Last observation/baseline observation carried forward.	**Weight loss (kg)**: Placebo: -1.4 (3.6); rimonabant: -5.3 (5.2) **Waist circumference (cm)**: Placebo: -1.9 (5.5); rimonabant: -5.2 (6.1) **Total cholesterol (mmol)**: Placebo: 0.10 (0.88); rimonabant: 0.04 (0.82) **Total cholesterol (%)**: Placebo: 3.3 (17.7); rimonabant: 2.0 (16.5) **non-HDL level (mmol)**: Placebo: 0.02 (0.85); rimonabant: -0.13 (0.80) **non-HDL level (%)**: Placebo: 2.5 (22.5); rimonabant: -1.8 (21.0) **HDL level (mmol)**: Placebo: 0.07 (0.15); rimonabant: 0.17 (0.20) **HDL level (%)**: Placebo: 7.1 (13.5); rimonabant: 15.4 (17.4) **LDL level (mmol)**: Placebo: 0.13 (0.76); rimonabant: 0.09 (0.79) **LDL level (%)**: Placebo: 7.2 (26.3); rimonabant: 6.9 (34.5) **Triglygerides (mmol)**: Placebo: 0.04 (0.87); rimonabant: -0.35 (1.28) **Triglygerides (%)**: Placebo: 7.3 (43.0); rimonabant: -9.1 (44.3) **Supine systolic BP (mmHg)**: Placebo: 1.6 (13.2); rimonabant: -0.8 (12.8) **Supine diastoic BP (mmHg)**: Placebo: -0.7 (8.4); rimonabant: -1.9 (8.2) **HbA_{1c} (%)**: Placebo: 0.1 (1.0); rimonabant: -0.6 (0.8) **Fasting glucose (mmol)**: Placebo: 0.33 (2.32); rimonabant: -0.64 (1.96) **Fasting insulin (µlU/mll)**: Placebo: 0.4 (14.8); rimonabant: -0.7 (9.9) **HOMA-IR**: Placebo: 0.6 (8.9); rimonabant: -0.5 (5.7) **Improved metabolic syndrome (%)**: Placebo: 18; rimonabant: 26 **Development of metabolic syndrome (%)**: Placebo: 38; rimonabant: 27 **hsCRP** (mg/L): Placebo: -0.0 (10.0); rimonabant: -1.4 (5.2) **Leptin (ng/ml)**: Placebo: 3.1 (7.5); rimonabant: -0.3 (6.0)

Description	Quality	Outcomes (ITT; LOCF) Change from baseline (95% CI)
Rio-North America[2] n=3045 Obese (BMI≥ 30 kg/m^2) or overweight (BMI≥ 27 kg/m^2) adults (>18 years) 5mg/day or 20mg/day rimonabant vs placebo Mean age: Placebo: 44.8 (SD: 11.6); 20mg rimonabant: 45.6 (SD: 11.8) Number male: Placebo: 113/607 (18.6%); 20mg rimonabant: 230/1219 (18.9%) Mean BMI: Placebo: 37.6 (SD: 6.4); 20mg rimonabant: 37.2 (SD: 6.2) All variables examined were similar at baseline	**Randomisation**: Predefined randomisation schedule; blocks of 5: 1 placebo, 2 5mg rimonabant, 2 20mg rimonabant. Patients receiving rimonabant re-randomised in 2nd year **Allocation concealment**: Not described **Blinding**: Double blind **Sample size calculation**: Yes **Withdrawals/dropouts**: *Year 1* completed by: Placebo: 51%; 20mg rimonabant: 55% *Year 2* completed by: Placebo+Placebo: 72%; 20mg rimonabant+Placebo: 69%; 20mg rimonabant+20mg rimonabant 77% **Analysis**: ITT of all patients who received at least 1 dose of their allocated placebo/treatment drug in the respective year. Last observation carried forward	**Year 1** (20mg rimonabant vs placebo or proportions) **Weight loss**: -4.7 (-5.4, -4.1); p<0.001 **Waist circumference**:-3.6 (-4.3, -2.9); p<0.001 **Any adverse event**: Placebo: 82%; rimonabant: 85.5% **Serious adverse event**: Placebo: 3.5%; rimonabant: 4.5% **Psychiatric adverse event (discontinued in study)**: Placebo: 2.3%; rimonabant: 6.2% **HDL level**: 7.2 (5.6, 8.9); p<0.001 **Systolic BP**: -0.2 (-1.4, 1.0); p=0.75 **Diastolic BP**: 0.2 (-0.6, 1.0); p=0.66 **Triglycerides:** -13.2 (-17.7, -8.7); p<0.001 **Fasting glucose**: -0.65 (-1.8, 0.51); p=0.27 **Fasting insulin**: -2.8 (-4.1, -1.5); p<0.001 **Insulin resistance**: -0.8 (-1.2, -0.4); p<0.001 **Year 2 (received same Rx both years)** **Weight loss**: -3.6 (-4.3, -3.0); p<0.001 **Waist circumference**: -2.8 (-3.6, -2.0); p<0.001 **Maintenance of weight loss**: Patients continuing rimonabant maintained weight and waist circumference loss; those re-randomised to placebo regained weight and waist circumference at end of year 2. **Any adverse event**: Placebo: 82.6%; rimonabant: 82.9% **Serious adverse event**: Placebo: 4.7%; rimonabant: 3.9% **Psychiatric adverse event (discontinued in study)**: Placebo: 1.3%; rimonabant: 2.1% **HDL level**: 6.3 (4.3, 8.3); p<0.001 **Systolic BP**: -0.3 (-1.6, 1.0); p=0.63 **Diastolic BP**: 0.1 (-0.8, 0.9); p=0.86 **Triglycerides**: -8.5 (-13.4, -3.7); p<0.001 **Fasting glucose**: -0.82 (-2.16, 0.51); p=0.23 **Fasting insulin**: -1.8 (-3.3, -0.4); p=0.01 **Insulin resistance**: -0.6 (-1.0, -0.1); p=0.01

Description	Quality	Outcomes (ITT; LOCF) Change from baseline (SD)
Rio-Lipids[4] n=1036 Obese (BMI≥ 30 kg/m^2) or overweight (BMI≥ 27 kg/m^2) adults (>18 years) 5mg/day or 20mg/day rimonabant vs placebo Mean age: Placebo: 47.0 (SD: 10.1); 20mg rimonabant: 48.4 (SD: 10.0) Number male: Placebo: 42.1%; 20mg rimonabant: 38.4% Mean BMI: Placebo: 34.0 (SD: 3.5); 20mg rimonabant: 33.9 (SD: 3.3)	**Randomisation**: Randomised in blocks of 3; 1:1:1 ratio. Method not described **Allocation concealment**: Method not described **Blinding**: Double blind **Sample size calculation**: No **Withdrawals/dropouts**: Completed by: Placebo: 40%; 20mg rimonabant: 40% **Analysis**: Last observation carried forward	**Weight loss (kg):** Placebo: -1.5 (5.0); rimonabant: -6.9 (6.1) **Waist circumference (cm):** Placebo: -2.4 (5.7); rimonabant: -7.1 (6.8) **Total cholesterol (%):** Placebo: 2.3 (14.2); rimonabant: 1.6 (14.4) **HDL level (%):** Placebo: 11.0 (15.8); rimonabant: 19.1 (20.9) **LDL level (%):** Placebo: 7.0 (22.4); rimonabant: 7.2 (28.4) **Peak size of LDL particles (A):** Placebo: -0.9 (3.9); rimonabant: 0.3 (3.8) **Proportion of small LDL (%):** Placebo: 3.2 (18.8); rimonabant: -1.5 (16.1) **Triglygerides (%):** Placebo: -0.2 (38.7); rimonabant: -12.6 (41.2) **Systolic BP (mmHg):** Placebo: -0.3 (10.1); rimonabant: -2.1 (12.3) **Diastolic BP (mmHg):** Placebo: -0.2 (7.4); rimonabant: -1.7 (8.5) **Heart rate (bpm):** Placebo: 0.7 (8.3); rimonabant: 0.9 (7.2) **Fasting glucose (mmol/l):** Placebo: -0.05 (0.62); rimonabant: -0.08 (0.58) **Fasting insulin (µIU/mll):** Placebo: 0.9 (15.9); rimonabant: -1.7 (12.4) **Adiponectin (µg/mll):** Placebo: 0.7 (1.9); rimonabant: 2.2 (2.5) **Leptin (ng/ml):** Placebo: -0.3 (6.0); rimonabant: -4.1 (7.4) **C-reactive protein (mg/ml):** Placebo: -0.4 (NR); rimonabant: -0.9 (NR)

Description	Quality	Outcomes (ITT; LOCF) Change from baseline (SD)
Rio-Europe[1] n=1507; n=920 at 1 year follow-up Obese (BMI≥ 30 kg/m^2) or overweight (BMI≥ 27 kg/m^2) adults (>18 years) 5mg/day or 20mg/day rimonabant vs placebo Mean age: Placebo: 45.0 (SD: 11.6); 20mg rimonabant: 44.6 (SD: 11.9) Number male: Placebo: 61 (20%); 20mg rimonabant: 121 (20%) Mean BMI: Placebo: 35.7 (SD: 5.9); 20mg rimonabant: 36.2 (SD: 5.8)	**Randomisation**: Centrally generated randomised code list; blocks of 5: 1 placebo, 2 5mg, 2 20mg rimonabant. **Allocation concealment**: Not reported **Blinding**: Double blind **Sample size calculation**: No **Withdrawals/dropouts**: Completed by: Placebo: 58%; rimonabant: 61% **Analysis**: Last observation carried forward	**Weight loss (kg):** Placebo: -1.8 (6.4); rimonabant: -6.6 (7.2) **Waist circumference (cm):** Placebo: -2.4 (6.9); rimonabant: -6.5 (7.4) **Fasting glucose (mmol/l):** Placebo: 0.03 (0.77); rimonabant: -0.09 (0.65) **Fasting insulin (µIU/mll):** Placebo: 1.8 (13.0); rimonabant: -1.0 (8.8) **Total cholesterol (mmol/l):** Placebo: 0.08 (0.78); rimonabant: 0.05 (0.70) **LDL level:** Placebo: 0.17 (0.70); rimonabant: 0.08 (0.63) **HDL level:** Placebo: 0.15 (0.23); rimonabant: 0.26 (0.26) **Systolic BP:** Placebo: 0.3 (12.3); rimonabant: -1.0 (12.5) **Diastolic BP:** Placebo: 0.1 (8.5); rimonabant: -0.9 (8.7) **HOMA-IR**: Placebo: 0.4 (3.5); rimonabant: -0.3 (2.4)

Description	Quality	Outcomes (ITT; LOCF) % change
REBA[6] n=156 Adults (>18 years) with BMI 30 to 45 kg/m^2 20mg/day rimonabant vs placebo with or without 600kcal deficit hypocaloric diet 3 month follow-up Mean age: Placebo: 45.0 (SD: 11.6); 20mg rimonabant: 44.6 (SD: 11.9) Number male: 21% Mean BMI: 36.5 kg/m^2	**Randomisation**: Centrally generated randomised code list; allocated 1:1:1:1. **Allocation concealment**: Not reported **Blinding**: Double blind **Sample size calculation**: No **Withdrawals/dropouts**: Completed by: Placebo: 95%; rimonabant: 88% **Analysis**: ITT – method not sepcified	**High Fat Meal (3/4 weeks):** **Energy intake:** Placebo: -9%; rimonabant: -17% **Carbohydrate intake (compared to placebo):** -16.1% **Fat intake (compared to placebo):** -16.9% **Protein intake (compared to placebo):** -17.6% **Low Fat Meal (3/4 weeks):** **Energy intake:** Placebo: +3.1%; rimonabant: -15.6% **Carbohydrate intake (compared to placebo):** -16.1% **Fat intake (compared to placebo):** -16.9% **Protein intake (compared to placebo):** -17.6% **Low Fat Meal (10/11 weeks):** **Energy intake:** Placebo: +2.8%; rimonabant: -16.7% **Total energy reduction:** Placebo: -8.8%; rimonabant: -23.2% **Change from baseline (3/4 weeks):** **Mean energy intake:** Placebo: -9.3%; rimonabant: -15.9% **Carbohydrate intake (compared to placebo):** -13.1% **Fat intake (compared to placebo):** -16.9% **Protein intake (compared to placebo):** -10.2% **Change from baseline (10/12 weeks):** **Mean energy intake:** Placebo: -6.5%; rimonabant: -13.3% **Weight loss (kg)(with diet):** Placebo: -1.69 (SD 3.37); rimonabant: -4.44 (SD 3.78) **Waist circumference (cm)(with diet):** Placebo: -3.3 (SD 4.89); rimonabant: -4.58 (SD 5.69)

Description	Quality	Outcomes (ITT; LOCF) Change from baseline (SD)
SERENADE[5] n=278 Overweight/obese patients with treatment naïve type-2 diabetes 20mg/day rimonabant vs placebo 6 month follow-up Mean age: Not reported Number male: Not reported Mean BMI: Not reported	**Randomisation**: Not reported **Allocation concealment**: Not reported **Blinding**: Double blind **Sample size calculation**: No **Withdrawals/dropouts**: Completed by: 85% **Analysis**: Not reported	**Weight loss (kg):** Placebo: -2.8 (4.8); rimonabant: -6.7 (5.5) **Waist circumference (cm):** Placebo: -2 (5); rimonabant: -6 (6) **HDL level (%):** Placebo: 3.2 (12.2); rimonabant: 10.1 (17.0) **Triglygerides (%)**: Placebo: 4.4 (58.1); rimonabant: -16.3 (32.8) **HbA_{1c} (%)**: Placebo -0.3 (1.2); rimonabant: -0.8 (1.2)

Table 4.2: Details of the three unpublished trials as provided by the manufacturer

Trial	Study Characteristics	Study Treatments Number of patients randomised Treatment duration	Outcome Measures
REBA EFC5031 Phase 3	A randomised, double-blind, placebo controlled, parallel group, 3 month trial of the energy intake effects and safety of SR141716 with, or without hypo calorific diet in obese subjects UK, multi-centre, randomised (concealed randomisation), double blind (identical matched placebo capsules), placebo controlled trial, parallel group study *Inclusion criteria* Obese Adults aged 18 years and above, Body mass index 30 and <45kg/m^2	Rimonabant 20mg n=38 (without hypo-calorific diet) Rimonabant 20mg n=38 (with hypo-calorific diet) Placebo n=38 (without hypo-calorific diet) Placebo n=38 (with hypo-calorific diet) Treatment duration: 12 weeks (1-4 weeks screening, 2 week single blind placebo run in, 12 week double blind treatment). Treatments administered once daily before breakfast	*Primary* • energy intake *Secondary* • satiety • food choice • feeling of control • craving *Clinical safety* • adverse events • vital signs • clinical laboratory evaluation
CRAVING ACT3801 Phase 3	Efficacy and safety of rimonabant on weight loss and frequency of binge episodes in obese patients International, multi-centre (US and Europe with UK centres), randomised (concealed randomisation), double blind (identical matched placebo capsules), placebo controlled, parallel group, efficacy study *Inclusion criteria* Obese Adults aged between 18 and 70 years, diagnosis of binge eating disorder using the questionnaire on eating and weight patterns (QEWP-T) for diagnosing eating behaviours, body mass index =>30 and <45kg/m^2.	Rimonabant 20mg n=143 (with hypo-calorific diet) Placebo n=146 (with hypo-calorific diet) Treatment duration: 6 months, 15 day screening, 6 month double blind treatment period. Study treatments given once a day before breakfast	P*rimary* • Change in body weight from baseline to day 180 visit *Secondary* • binge eating episodes • binge eating scale • TFEQ dimensions • waist circumference • body mass index *Clinical safety* • clinical examination • vital signs • adverse events • clinical laboratory evaluation • hospital anxiety & depression scale (HAD
CLAMP EFC5745 Phase 3	[redacted]	[redacted]	[redacted]

4.1.4 Details of any relevant studies that were not included in the submission ?

The ERG's searches did not identify any further published trials of rimonabant. However, the ERG is aware of a number of ongoing trials; it is not clear whether interim data are available for these trials. As data from three as yet unpublished trials conducted by the manufacturer (EFC5031, EFC5745 and ACT3801) are included in the submission, it is not clear if data available from other unpublished trials were not included in the manufacturer's submission.

Given the time constraints imposed, the ERG did not attempt to identify all the relevant orlistat and sibutramine trials available in the published literature, but have used the NICE guidelines to inform their report.[7] It has not been possible, however, to establish the reliability of the manufacturer's review of orlistat and sibutramine.

4.1.5 Description and critique of manufacturer's approach to validity assessment

The manufacturer used appropriate criteria to assess the quality of the RIO trials. Details of the quality assessment of the REBA trial, or the trials cited in table footnotes (EFC5745 and ACT3801), were not provided in the initial submission. Brief study details and methods for randomisation and allocation concealment were provided on request by the ERG; these seemed adequate for all three trials. Neither the dropout rates, nor the basis for the sample size calculations were provided by the manufacturer for these trials. There are a number of discrepancies between the validity assessment provided in the submission and the information available in published trial reports. These discrepancies are primarily information that is lacking in the published papers, relating principally to adequacy of allocation concealment and power calculations, which is reported in the manufacturer's submission. It is assumed that these discrepancies stem from access to full trial reports that included unpublished detail of trial methodology.

4.1.6 Description and critique of manufacturer's outcome selection

The final scope issued by NICE stated that the outcomes to be considered were: weight loss; waist circumference; maintenance of weight loss; adverse effects of treatment; health-related quality of life; and mortality. Further consideration could also be given to surrogate outcomes, including: cholesterol levels and lipid profiles (including LDL and HDL); blood pressure; cardiovascular events and associated reduction in cardiovascular interventions; and the prevention and control of type 2 diabetes. These outcomes were addressed in the manufacturer's submission. No direct data for cardiovascular event rates were presented, with this being evaluated using surrogate outcomes.

Although data relating to HRQoL and adverse events were presented for rimonabant compared to placebo, no such data were presented for orlistat or sibutramine. Given the different results found for the RIO trials between the IWQoL and the SF-36, and the frequency and variety of adverse events associated with these three drugs, a comparison of HRQoL and adverse events data would have been informative. A full summary of adverse event data for orlistat/sibutramine was requested by the ERG, but not provided.

4.1.7 Describe and critique the statistical approach used

4.1.7.1 Handling of missing data

The manufacturers used a last observation carried forward (LOCF) to deal with the dropouts. However, to investigate the impact of such high drop out rates further (ranging from 23% to 60% across the RIO trials), a best case/worst case scenario may have been appropriate given that many patients may have dropped out due to lack of success and loss of motivation. The manufacturer was requested by the ERG to justify the sole use of LOCF in their submission. The manufacturer provided further details relating to the use of LOCF, and tables of the results from each of the RIO trials as analysed using LOCF, baseline observation carried forward, and repeated measures. The ERG were satisfied that the LOCF provided conservative results for each outcome.

In addition, on request of the ERG, the manufacturer provided the dropout rates for the included orlistat and sibutramine, to give an indication as to whether a LOCF would have been applied to a similar proportion of patients across the trials. The dropout rates for studies of 1 year duration were reported as 8% to 50% for orlistat (4% to 54% for placebo) and 8% to 49% for sibutramine (11% to 51% for placebo). The lowest dropout rates for orlistat and placebo were the same trial;[16] dropout rates in other orlistat trials was more comparable to those reported in the RIO trials.

Figures 5 and 7 in the manufacturer's original submission clearly show 100% of patients recruited to the RIO-Europe and RIO-Diabetes trials were included in the analysis, and therefore an intention to treat (ITT) analysis conducted. However, Figure 4 shows that the ITT analysis for RIO-North America was not complete, and the reason for this is not immediately apparent. It is not clear from Figures 6 and 8 what proportion of patients were included in the ITT analysis for RIO-Lipids and SERENADE. A figure was not provided for the REBA trial, either in the original submission or subsequent resubmission.

From the methods reported by the manufacturer, it is not clear whether data extraction was conducted in duplicate, or whether extracted data was checked by an independent reviewer; the discrepancies highlighted reduce the confidence in both the acquisition, and use, of the data from orlistat and sibutramine. .

Given the time constraints, the ERG were unable to check the data extraction for the other orlistat and sibutramine tirals, and therefore given the uncertainty outlined above, the ERG are unable to comment on the comparability of dropout rates between the rimonabant and the orlistat/sibutramine trials. However, despite this, given the difficulty with defining an appropriate best case scenario, the ERG was satisfied that the use of LOCF used by the manufacturer was appropriate.

4.1.7.2 Weight loss data

In the submission, the effectiveness of rimonabant focussed on evidence from placebo-controlled trials of rimonabant, mainly the four RIO trials sponsored by the manufacturer: RIO–North America, RIO-Europe, RIO-Diabetes and RIO-Lipids. The data from these four trials were presented by trial in tables as placebo-subtracted values (i.e. relative risks (RR) for dichotomous data or mean differences for continuous data). Data for many outcomes were presented (most primary and secondary outcomes) for change from baseline to 1 year (ITT and completers analysed separately) and for change from baseline to 2 years (ITT and completers separately). In these tables the weight loss-related outcomes presented were change in body weight, proportion of participants losing 5% of body weight, proportion of participants losing 10% of body weight and change in waist circumference. Change in BMI from baseline was not included in these tables, but was provided on ERG request.

The ERG questioned whether this analysis was sufficiently detailed and the manufacturer provided a stratified analysis of primary outcomes according to baseline BMI.

The focus of the submission on the treatment effect relative to placebo, with absolute effect data provided in the appendices, makes it difficult to get a clear understanding of the clinical benefit of rimonabant. The ERG has brought some of the absolute data into the body of this report to help with this.

4.1.7.3 Health related quality of life data

Data from two separate instruments, the obesity specific Impact of Weight on Quality of Life-Lite (IWQOL-Lite) and the generic Medical Outcomes Study Short Form 36 (SF-36), were presented. Data were available for the RIO-North America, RIO-Europe, RIO-lipids and RIO-diabetes trials at 1 year, presented as change from baseline (ITT data), and from RIO-North America and RIO-Europe at 2 years, presented as unadjusted and adjusted mean differences. Utility scores were calculated from the data available on both

instruments using the SF6D algorithm using the methods described by Brazier (2002 and 2004).[17, 18]

A pooled analysis for IWQOL-lite and SF-36 scores was presented. Methods used in these pooled analysis are not described in detail; a study fixed effect was added as covariate for the pooled analysis. The manufacturers accounted for differences in baseline values using ANCOVA.

When evaluating HRQoL, the manufacturer states that respondents had to answer at least 50% of the items in a multi-items scale, for a score to be calculated. There was no indication given as to the number of respondents who did not provide sufficient information. From the number of patients reported in the results tables, it appears 80% to 92% of patients provided data for the IWQoL-lite, and 76% and 93% for SF-36, depending on the domain.

4.1.7.4 Meta-analysis of weight loss and cardiovascular and diabetes risk-related outcome data

Standard meta-analyses techniques were used to pool weight loss-related data. A fixed effect model was used when the p-value of the Chi-squared test for heterogeneity was $\geq$0.1, and a random effects model when the p-value was <0.1. An *a priori* decision was made that patients with diabetes were too clinically different from other overweight or obese patients to be included in the main meta-analyses of weight loss-related data. Thus data from Rio-North America, RIO-Europe and RIO-Lipids were pooled, and data from RIO-diabetes presented separately. Clinical advice to the ERG confirms that presenting the results separately for a diabetic sub-group was appropriate, but presenting results for the whole population would also be appropriate. NICE also suggest that less strict goals may be appropriate for patients with diabetes, as weight loss may be slower in these patients.[7]

It appears that the rationale for separating the diabetic subgroup in the evaluation of effectiveness, was not applied when pooling HRQoL data, with all four RIO studies being pooled together. It seems likely that similar heterogeneity would exist for at least some domains of the HRQoL tools

between diabetic and non-diabetic population. The ERG has rerun the meta-analyses for the primary weight loss outcomes (except for BMI as insufficient data were provided in both the original submission and in the clarification submission).

In addition to the meta-analyses based on published data, the manufacturer also provided pooled patient-level data. They provided these for non-diabetic patients (Rio-North America, RIO-Europe and RIO-Lipids) and for treated dyslipidaemics (Rio-North America, RIO-Europe).

4.1.7.5 Analysis of orlistat and sibutramine trials

The ERG found the presentation of the data for orlistat and sibutramine unclear. It is difficult to understand the breakdown of the populations, and how these relate to the base-case analyses used in the economic model. Furthermore, it is not clear where the data for these separate base case analyses originates from and how much data contributes to each. Checking of the appendices by the ERG found that results for orlistat presented in Table 21 of the submission are supported by the trials listed in Appendix Table 70. However, the results for sibutramine presented in Table 22 are based on only three trials, none of which contributes to the summary of data for non-diabetics; it is unclear how the figures reported in this column of the table were derived. Overall the confusing presentation of the data and analyses relating to orlistat and sibutramine, and discrepancies noted in the data for orlistat and sibutramine by the ERG, undermines confidence in the review findings.

4.1.7.6 Comparison of rimonabant with orlistat and sibutramine

Given the lack of head-to-head trials comparing rimonabant with the active comparators orlistat and sibutramine, the use of indirect comparisons was the only option to investigate the difference in effectiveness between rimonabant and orlistat/sibutramine. However, although the manufacturer provides a section devoted to these methods, the comparison was a superficial tabulation of the relative effects of the three drugs each compared to placebo, with no statistical analysis of the relative effect of rimonabant compared to

orlistat/sibutramine using placebo as the common comparator. The manufacturer was requested by the ERG to provide a full indirect comparison, or pairwise comparisons for the primary outcomes; some pairwise comparisons were provided.

4.1.8 Summary statement

The evaluation of rimonabant was reasonably well presented, with clear and appropriate inclusion criteria. However, some aspects of the review process were not completely reported. Insufficient details were provided in the original submission relating to the ongoing studies from which data was derived; some further details were provided on ERG request. The analysis of the evidence comparing rimonabant to placebo was extensive, although there was some inconsistency between outcomes presented at different points in the submission. Importantly, the rationale for, and composition of, some sub-groups was also unclear, reflecting the RIO trials rather than the product licence and the use of these drugs in clinical practice.

The review of the two active comparators, orlistat and sibutramine, was not clearly presented, particularly in the case of sibutramine where it is not clear from where the data presented were derived. In addition, the comparisons between rimonabant and orlistat/sibutramine could have been more extensive, particularly in relation to adverse events, HRQoL, and the comparison between rimonabnat and orlistat, where a comparison of outcomes at 2 years would have been informative.

4.2 Summary of submitted evidence

4.2.1 Efficacy

The four RIO trials (6600 patients) demonstrated consistent and significant reductions in body weight at one year compared with diet and exercise alone. There were significantly more responders achieving ≥5 and ≥10% weight loss compared with placebo. The number needed to treat (NNT) to achieve a ≥5% weight loss is 3 in both non-diabetic and diabetic populations, and between 4 and 7 for a ≥10% weight loss response.

Treatment with rimonabant also results in significant and consistent improvements in some of the cardiovascular and diabetes risk factors associated with obesity, namely, impaired glycaemic control, raised triglycerides, and reduced HDL-C.

Weight loss and improvements in associated cardiovascular and diabetes risk factors are maintained over 2 years when rimonabant is continued, however, the relative effect over placebo is lower in year 2 . Following withdrawal of rimonabant treatment at 1 year, there was a gradual reduction in the rate of weight loss until there was no difference from placebo at two years.

4.2.2 Safety

During the first year of treatment, a total of thirteen treatment emergent adverse events (TEAEs) in the rimonabant group were reported with an increase in frequency of >1% more than the placebo group, including nausea; diarrhoea; vomiting; dizziness; anxiety; insomnia; mood alterations with depressive symptoms; depressive disorders; influenza; asthenia/fatigue; gastroenteritis; contusion, and hot flushes. These events were generally of mild or moderate intensity, non-serious, transient, and resolved spontaneously or within a primary care setting, while patients remained on treatment.
TEAEs of special interest include depression and suicidality. Depressive disorders or mood alterations with depressive symptoms and suicidal ideation have been reported in patients receiving rimonabant 20mg.

4.2.3 Quality of life (QoL)

The two QoL instruments used in the trial programme reported differing results. Compared to placebo at one year; IWQoL-Lite (disease-specific) shows significant positive improvements in most domains for rimonabant compared with placebo, whilst SF-36 (generic) found a significant improvement in physical functioning and general health, but a significantly adverse effect on mental health..

4.2.4 Comparison of rimonabant with. orlistat and sibutramine

In the submission rimonabant is compared with orlistat and Sibutramine. Indirect pairwise comparisons indicate that in a non-diabetic population, weight related outcomes at one year for rimonabant are statistically significantly more beneficial than orlistat. In diabetic patients only the proportion of responders (5% or 10% body weight loss) was significantly greater with rimonabant. The comparison of rimonabant and Sibutramine found little difference, with only the proportion of patients achieving 5% body weight loss being significantly higher on rimonabant.

4.3 Critique of submitted evidence

4.3.1 Efficacy of rimonabant

The efficacy of rimonabant was evaluated using data from four placebo controlled trials, RIO-Europe, RIO-North America, RIO-Diabetes and RIO-Lipids. The one year intention to treat (ITT) data for the primary variables are summarised in Tables 4.3 and 4.4. These tables were generated by the ERG from data provided in the body of the submissions, appendices of the original submission and in the clarification submission in order to present a clear summary of the relative and absolute weight effects of rimonabant at one year.

Table 4.3: Pooled estimates of effect for changes from baseline to 1 year

	Meta-analysis results using trial data		
	All RIO trials	**Non-diabetics (RIO-NA/RIO-EU/RIO-Lipids)**	**Diabetics (RIO-Diabetes)**
Change in weight (kg) (WMD [95% CI])	-4.61 [-4.96, -4.25]*	-4.91 [-5.35, -4.48]	-3.90 [-4.57, -3.23]
Proportion of patients losing 5% body weight (RR [95% CI])	2.72 [2.44, 3.04]	2.61 [2.32, 2.95]	3.41 [2.58, 4.50]
Proportion of patients losing 10% body weight (RR [95% CI])	3.73 [3.07, 4.54]*	3.48 [2.84, 4.27]	8.07 [3.37, 17.46]
Change in waist circumference (cm) (WMD [95% CI])	-3.84 [-4.27, -3.42]	-4.01 [-4.50, -3.53]	-3.30 [-4.17, -2.43]
BMI (kg/m^2) (WMD [95% CI])	Data not provided	-1.76 [-1.92, -1.60][$]	-3.90 [-4.57, -3.23]

*subject to significant statistical heterogeneity [$]summary of IPD not from published sources

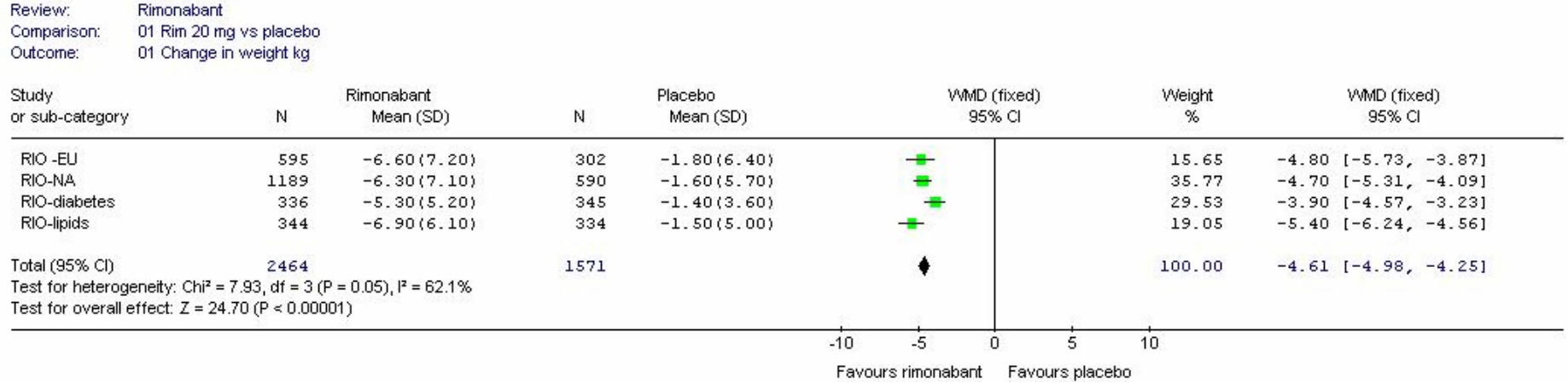
The individual trial data and the pooled estimates of effect showed that rimonabant resulted in a significantly greater benefit than placebo in terms of all primary weight loss outcomes.

Table 4.4: Summary of placebo-subtracted changes from baseline to year 1: ITT data for RIO studies for all outcomes

Trial	**RIO-North America**[2]	**RIO-Europe**[1]	**RIO-Lipids**[4]	**RIO-Diabetes**[3]
n [Placebo;rimonabant 20mg]	**590;1189**	**302;595**	**334;344**	**345;336**
Body weight (kg) mean changes from baseline (SD)	-6.3 (7.1) vs -1.6 (5.7)	-6.6 (7.2) vs -1.8 (6.4)	-6.9 (6.1) vs -1.5 (5.0)	-5.3 (5.2) vs -1.4 (3.6)
Difference in the mean change from baseline vs. placebo [95% CI]	-4.70 [-5.31;-4.09]	-4.80 [-5.73;-3.87]	-5.40 [-6.24;-4.56]	-3.90 [-4.57;-3.23]
Patients who achieved ≥5% body weight loss n/N (%)	578/1189 (48.6) vs 118/590 (20)	303/595 (50.9) vs 58/303 (19.1)	201/344 (58.4) vs 65/334 (19.5)	166/336 (34.5) vs 50/345 (14.5)
Relative risk [95% CI]	2.43 [2.05; 2.89]	2.65 [2.08; 3.39]	3.00 [2.37; 3.80]	3.41 [2.58; 4.50]
Patients who achieved ≥10% body weight loss n/N (%)	300/1189 (25.2) vs 50/590 (8.5)	163/595 (27.4) vs 22/302 (7.3)	112/344 (32.6) vs 24/334 (7.2)	55/336 (16.4) vs 7/345 (2.0)
Relative risk [95% CI]	2.98 [2.24; 3.95]	3.76 [2.46; 5.74]	4.53 [2.99; 6.86]	8.07 [3.73; 17.46]
Waist circumference (cm) Mean change from baseline	-6.1 (7.1) vs -2.5 (6.9)	-6.6 (7.4) vs -2.4 (6.9)	-7.1 (6.8) vs -2.4 (5.7)	-5.2 (6.1) vs -1.9 (5.5)
Difference in the mean change from baseline vs. placebo [95% CI]	-3.60 [-4.29; -2.91]	-4.10 [-5.08; -3.12]	-4.70 [-5.64; -3.76]	-3.30 [-4.17; -2.43]
BMI (kg/m^2)* Difference in the mean change from baseline vs. placebo [95% CI]	-1.70 [-1.92; -1.48]	-1.70 [-2.03; -1.37]	-2.00 [-2.30; -1.70]	-1.40 [-1.63; -1.17]

* Data by treatment group nor pooled result provided

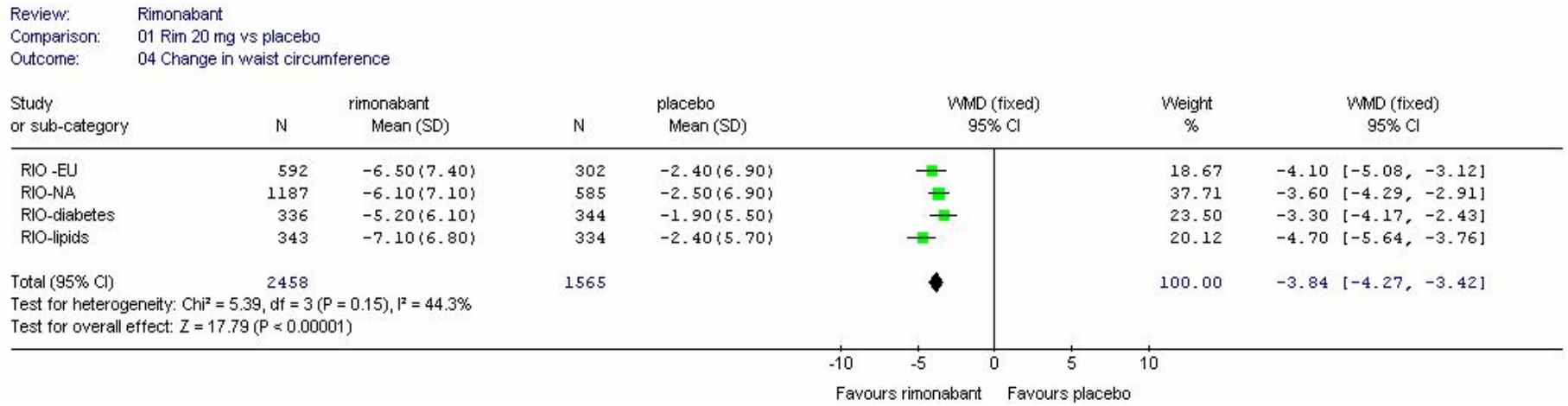
Figure 4.1: Meta-analyses of primary weight loss variables for change from baseline to 1 year (ITT data) (ERG generated)
Change in weight (kg)



Proportion of patients achieving 5% weight loss
Figure removed academic-in-confidence

Proportion of patients achieving 10% weight loss
Figure removed academic- in-confidence

Change in waist circumference



The mean data presented in Table 4.4 show that, whilst treatment with rimonabant is statistically significantly better than placebo, the absolute mean weight loss at one year is between 6.3 and 6.9 Kg (5.3 in RIO-diabetes), reduction in waist circumference between 6.1 and 7.1 cm and a reduction in BMI between 1.7 and 2.0 kg/m^2.

The forest plots of the meta-analysis of all four RIO trials (generated by the ERG) are presented in Figure 4.1.

The meta-analysis including all RIO trials run by the ERG demonstrates that the *a priori* decision by the manufacturer not to include the RIO-diabetes trial was justified statistically as well as clinically, with two of the four outcomes being subject to significant statistical heterogeneity. However, although the mean weight loss and placebo subtracted reduction in BMI in the RIO-diabetes trial were slightly lower than in the other RIO trials, the other primary outcomes did not indicate any materially different treatment effect in this population.

Table 4.5 shows the pooled results of other reported outcomes as presented in the original company submission. These results indicate that rimonabant does not appear to have any adverse effect on cardiovascular or diabetes risk factors and has statistically significant beneficial effects on SBP (summary data only), HDL-cholesterol, triglycerides and fasting plasma glucose in both diabetic and non-diabetic patients (summary data only), and HbA_{1c} in diabetic patients.

Table 4.5: Secondary outcomes from the RIO trials as reported in the manufacturer's original submission

	Meta-analysis results using trial data (WMD [95% CI])		Pooled patient-level data (Mean [95% CI])	
	Non-diabetics	Diabetics	Non-diabetics	Treated dyslipidaemics
Change in systolic BP (mmHg)	-0.87 [-1.72, -0.02]	-2.40 [-4.35, -0.45]	[redacted]	[redacted]
Change in diastolic BP (mmHg)	-0.50 [-1.09, 0.09]	-1.20 [-2.45, 0.05]	[redacted]	[redacted]
Change in total plasma cholesterol (mmol/L)	-0.02 [-0.07, 0.03]	-0.06 [-0.19, 0.07]	[redacted]	[redacted]
Change in LDL-C (mmol/L)	-0.04 [-0.09, 0.01]	-0.04 [-0.16, 0.08]	[redacted]	[redacted]
Change in HDL-C (mmol/L)	0.09 [0.08, 0.11]	0.10 [0.07, 0.13]	[redacted]	[redacted]
Change in triglycerides (mmol/L)	-0.21 [-0.27, -0.16]	-0.39 [-0.56, -0.22]	[redacted]	[redacted]
Change in HbA_{1c} (%)	-	-0.70 [-0.84, -0.56]	[redacted]	[redacted]
Change in fasting plasma glucose (mmol/L)	-0.05 [-0.10, -0.01]	-0.97 [-1.30, -0.64]	[redacted]	[redacted]

4.3.1.1 Analysis by BMI

The ERG felt that a stratified analysis according to BMI would be important to identify potential heterogeneity in response to rimonabant between BMI categories. To address this, following a request from the ERG, the manufacturer provided more information regarding baseline BMI (Table 4.6) and a re-analysis of the data by BMI (Table 4.7).

Table 4.6: Baseline mean BMI data and the proportion of patients categorised to each BMI group, for the four RIO trials as presented in the manufacturers submission

BMI (kg/m^2)	RIO-North America[2]		RIO-Europe[1]		RIO-Lipids[4]		RIO-Diabetes[3]	
	Rimonabant (n=1219)	Placebo (n=607)	Rimonabant (n=599)	Placebo (n=305)	Rimonabant (n=346)	Placebo (n=342)	Rimonabant (n=339)	Placebo (n=348)
Mean (SD)	37.2 (6.2)	37.6 (6.4)	36.2 (5.8)	35.7 (5.9)	33.1 (3.3)	33.3 (3.4)	33.6 (3.6)	33.7 (3.6)
>25* - <30	62 (5.1)	30 (4.9)	61 (10.2)	45 (14.8)	68 (19.7)	62 (18.1)	65 (19.2)	67 (19.3)
≥30 - <35	471 (38.6)	221 (36.4)	241 (40.2)	118 (38.7)	175 (50.6)	163 (47.7)	139 (41.0)	145 (41.7)
≥35 - <40	341 (28.0)	180 (29.7)	157 (26.2)	80 (26.2)	99 (28.6)	110 (32.2)	127 (37.5)	132 (37.9)
≥40	344 (28.2)	176 (29.0)	139 (23.2)	62 (20.3)	4 (1.2)	7 (2.1)	8 (2.4)	4 (1.2)

* Characterised as <30 in the RIO Programme

Table 4.7: Summary of placebo-subtracted changes from baseline to year 1 for the primary outcomes, stratified by baseline BMI, using ITT data for the Rio trials (n=rimonabant/placebo)

	Rio-North America[2]					Rio-Europe[1]				
	All	<30 kg/m^2	30-<35 kg/m^2	35-<40 kg/m^2	>40 kg/m^2	All	<30 kg/m^2	30-<35 kg/m^2	35-<40 kg/m^2	>40 kg/m^2
Body weight (kg) Difference in mean change from baseline vs. placebo [95% CI]										
BMI (kg/m^2) Difference in mean change from baseline vs. placebo [95% CI]										
Waist circumference (cm) Difference in mean change from baseline vs. placebo [95% CI]										
Patients achieved ≥5% body weight loss. Relative risk [95% CI]										
Patients achieved ≥10% body weight loss. Relative risk [95% CI]										
	Rio-Lipids[4]					Rio-Diabetes[3]				
	All	<30 kg/m^2	30-<35 kg/m^2	35-<40 kg/m^2	>40 kg/m^2	All	<30 kg/m2	30-<35 kg/m2	35-<40 kg/m2	>40 kg/m2
Body weight (kg) Difference in mean change from baseline vs. placebo [95% CI]										
BMI (kg/m^2) Difference in mean change from baseline vs. placebo [95% CI]										
Waist circumference (cm) Difference in mean change from baseline vs. placebo [95% CI]										
Patients achieved ≥5% body weight loss. Relative risk [95% CI]										
Patients achieved ≥10% body weight loss. Relative risk [95% CI]										

The data in Table 4.6 shows clearly that the estimates of mean BMI in the RIO-North America and RIO-Europe trials were similar, and that those in the RIO-Lipids and RIO-diabetes trials were somewhat lower and less variable. This is to be expected given that patients with diabetes or dyslipidaema would be treated for obesity at lower BMI levels than patients without these risk factors. When categorised into the four main BMI groups, it can be seen that the bulk of the data is applicable to the ≥30-35 group, with ≥35-40 also well represented. The BMI group >25-<30 is particularly poorly represented in the RIO-North America trial, and is also underrepresented in the RIO-Europe and RIO-Lipids trials; the >40 group is particularly poorly represented in the RIO-Lipids and RIO-Diabetes trials.

Analyses by BMI were provided for each RIO trial individually, but not for the pooled 'non-diabetic' population. These analyses indicates that [redacted]. Thus the relative effect of rimonabant appears to be [redacted]

In summary, for any baseline BMI, the average weight loss beyond that which can be achieved with diet and exercise over a one year period is [redacted] with a [redacted] in BMI of [redacted].

4.3.1.2 Proportion of patients achieving at least a 5% or 10% loss of body weight

Patients achieving at least 5% or 10% loss of body weight is a marker of efficacy of weight loss drugs.[14] The numbers of patients achieving these levels of weight loss were higher with rimonabant than placebo (Table 4.8). The numbers needed to treat were calculated by trial and presented in the manufacturer's submission. All four RIO trials indicated that, for one person to lose 5% body weight at one year, 3 patients would have to be treated with rimonabant. For one person to lose 10% body weight at one year, 4 (RIO-

Lipids), 5 (RIO-Europe), 6 (RIO-North America) or 7 (RIO-Diabetes) patients have to be treated with rimonanbant.

In the manufacturer's submission, patients who achieved a 5% loss of body weight were classed as responders. Simple cumulative totals were used to calculate percentage responder rates across the trials. The crude pooled one year 5% response rate across all trials was used in the manufacturer's model (i.e. 50.6% (1248/2464) for rimonabant compared to 18.5% (291/1572) for diet and exercise placebo (p28 of clarification submission)). The cumulative responder rates were presented as a Kaplan-Meier response curve (Figure 4.2). These curves indicate that the [redacted]. This would suggest that [redacted]. Further data regarding response rates at different time points i.e. 3, 6 and 9 months would help clarify this.

Table 4.8: The number (%) of patients that achieved a 5% or 10% weight loss at 1 year in the RIO trials

	RIO- North America[2]		Rio-Europe[1]		Rio-Lipids[4]		RIO-Diabetes[3]	
	Rimonabant (n=1189)	Placebo (n=590)	Rimonabant (n=595)	Placebo (n=302)	Rimonabant (n=344)	Placebo (n=334)	Rimonabant (n=336)	Placebo (n=345)
5% achieved	[redacted]							
10% achieved	[redacted]							

The ERG requested the outcome measures for those patients that had achieved at least a 5% and 10% weight loss. These analyses were provided for each RIO trial individually, but not for the pooled 'non-diabetic' population. The reduction in the numbers of patients in these separate analyses resulted in a reduction of power. Undertaking these analyses with the pooled results for the non-diabetic population of the RIO trials would have increased their power and reliability of the results. Table 4.9 provides the data for the primary outcomes for the four RIO trials, with results for all participants, those that achieved ≥5% weight loss and those that achieved ≥10% weight loss reported separately as per the manufacturer's submissions. The numbers included in the analyses are indicated at the head of the column, unless otherwise stated.

Figure 4.2: Cumulative responder rates (≥5% body weight loss response criteria) during year 1 as presented by the manufacturer (Pooled ITT data from RIO-North America, RIO-Europe, RIO-Lipids)

Figure removed-academic in confidence

Table 4.9: Summary of placebo-subtracted changes from baseline to year 1, using ITT data for all patients in the Rio trials, those that achieved ≥ 5% weight loss, and those that achieved ≥10% weight loss

	Rio-North America[2]			**Rio- Europe**[1]		
	All Placebo n=590 Rimonabant n=1189	**5%** Rimonabant n	**10%** Placebo n Rimonabant n	**All** Placebo n Rimonabant n	**5%** Placebo n	**10%** Placebo n Rimonabant n
Body weight (kg) Difference in the mean change from baseline vs. placebo [95% CI]	-4.70 [-5.31;-4.09]	Placebo n		-4.80 [-5.73;-3.87]	Rimonabant n	
Waist circumference (cm) Difference in the mean change from baseline vs. placebo [95% CI]	-3.60 [-4.29; -2.91]	Placebo n		-4.10 [-5.08; -3.12]	Rimonabant n	
BMI (kg/m^2) Difference in the mean change from baseline vs. placebo [95% CI]	-1.70 [-1.92; -1.48]			-1.70 [-2.03; -1.37]		
Patients who achieved ≥5% body weight loss. Relative risk [95% CI]	2.43 [2.05; 2.89]			2.65 [2.08; 3.39]		
Patients who achieved ≥10% body weight loss. Relative risk [95% CI]	2.98 [2.24; 3.95]			3.76 [2.46; 5.74]		
	Rio-Lipids[4]			**Rio-Diabetes**[3]		
	All Placebo n=334 Rimonabant n=344	**5%** Placebo n	**10%** Placebo n Rimonabant n	**All** Placebo n=345 Rimonabant n=336	**5%** Placebo n Rimonabant n	**10%** Placebo n Rimonabant n
Body weight (kg) Difference in the mean change from baseline vs. placebo [95% CI]	-5.40 [-6.24;-4.56]	Rimonabant n		-3.90 [-4.57;-3.23]		
Waist circumference (cm) Difference in the mean change from baseline vs. placebo [95% CI]	-4.70 [-5.64; -3.76]	Rimonabant n		-3.30 [-4.17; -2.43]		
BMI (kg/m^2) Difference in the mean change from baseline vs. placebo [95% CI]	-2.00 [-2.30; -1.70]			-1.40 [-1.63; -1.17]		
Patients who achieved ≥5% body weight loss. Relative risk [95% CI]	3.00 [2.37; 3.80]			3.41 [2.58; 4.50]		
Patients who achieved ≥10% body weight loss. Relative risk [95% CI]	4.53 [2.99; 6.86]			8.07 [3.73; 17.46]		

Clinical advice also suggested that benefits of weight loss start to become apparent at a 5% weight loss, with benefits becoming more evident at 10% weight loss and over. When comparing the results for all patients with those who achieved 5% and 10% weight loss, it can be seen that all four trials reported [redacted] in body weight and waist circumference with rimonabant when all patients are included in the analyses. However, only two trials report [redacted] in body weight with rimonabant in those who had achieved 5% weight loss. [redacted] of the trials reported [redacted] in body weight with rimonabant in those who had achieved 10% weight loss, or in waist circumference in those who had achieved 5% or 10% weight loss.

4.3.1.3 Two year data

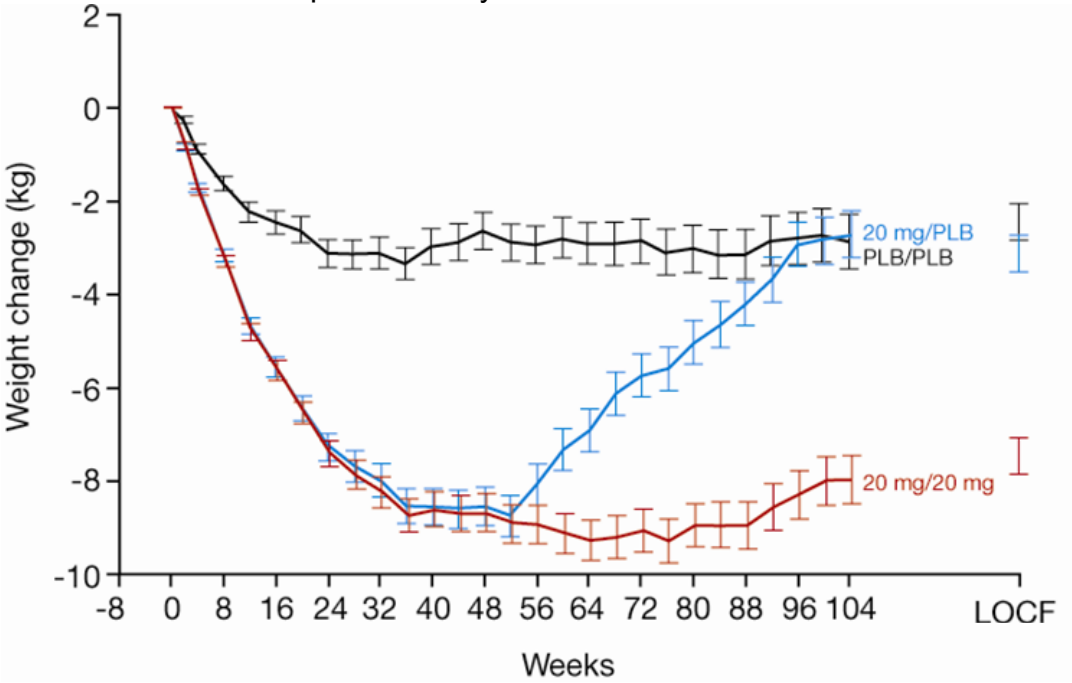
Only two of the RIO trials reported weight loss data at 2 years (RIO-North America and RIO-Europe). The primary outcomes as reported by the manufacturer for the ITT population are presented in Table 4.10. It is not clear which patients were included in the analyses of 2-year data from the RIO-North America trial. According to the revised flow diagram, 1219 patients were recruited and allocated to receive 20mg rimonabant in year 1. At the beginning of year 2, 660 of these patients remained in the trial and were re-randomised; 327 received placebo and 333 continued to receive 20mg rimonabant. Of the 33 patients receiving rimonabant for 2 years, 257 completed the trial and 328 were included in the year 2 analysis. According to the table, 864 patients prescribed 20mg of rimonabant were included in the analysis at the end of year 2

Table 4.10: Weight loss data at 2 years in the RIO-North America and RIO-Europe trials (ITT data)

Trial **n [Placebo;rimonabant 20mg]**	**RIO-North America** **590;864**	**RIO-Europe** **302;595**
Body weight (kg) Difference in mean change from baseline vs. placebo [95% CI]	-3.60 [-4.28; -2.92]	-4.30 [-5.29; -3.31]
Waist circumference (cm) Difference in mean change from baseline vs. placebo [95% CI]	-2.80 [-3.57; -2.03]	-3.90 [-4.89; -2.91]
BMI (kg/m^2) Difference in mean change from baseline vs. placebo [95% CI]	[redacted]	[redacted]
Patients who achieved ≥5% body weight loss Relative risk [95% CI]	2.05 [1.71; 2.47]	2.85 [2.16; 3.76]
Patients who achieved ≥10% body weight loss Relative risk [95% CI]	1.98 [1.46; 2.70]	3.50 [2.21; 5.55]

Over the second year, patients who remained on rimonabant maintained their weight loss although the effects relative to placebo were slightly lower at year 2 than at year 1. However, patients in the RIO-North America trial who were re-randomised to placebo for the second year had a gradual reduction in the rate of weight loss until there was no difference between these patients and patients who had received placebo for two years (Figure 4.3). Interestingly, according to Figure 4.3, the change from baseline in patients prescribed rimonabant 20mg is between 8 and 10 kg at 1 year. However the reported changes in baseline (Table 4.3) are -6.3 (SD: 7.1) for rimonabant 20mg and -1.6 (SD: 5.7) for placebo, showing an inconsistency between these data.

Figure 4.3: The change in the rate of weight loss over two years in the RIO-North America trial[2] as presented by the manufacturer



4.3.2 Adverse events associated with rimonabant

The manufacturer's submission refers to the safety database for rimonabant and cites the EMEA report on safety, which included 7447 patients exposed to 20 mg rimonabant daily for up to two years (a total of 3478 patient years). The submission however, focuses on the seven obesity trials: the four RIO trials; REBA (energy consumption); EFC5745 (insulin resistance); and ACT3801

(binge eating). All two-year data were derived from the RIO-North America and RIO-Europe trials. The manufacturers stated that there were 13 adverse events associated with rimonabant at a rate of ≥2%, and at a rate of at least 1% greater than placebo. Table 4.11 provides the rates of these adverse events as presented by the manufacturer.

There seems to be some discrepancies in the number of patients available to inform on adverse events, and the number of adverse events in the original submission. In the text (p69) the manufacturer indicates that there were 59 completed clinical trials involving more than 15,000 participants, and a total of 12,836 patients were exposed to rimonabant in phase III studies; 7,447 of which received rimonabant 20 mg for up to 2 years. It is therefore unclear why, in the table, the adverse event rates are based upon only 2742 patients receiving rimonabant 20 mg at 1 year, and 688 patients receiving rimonabant 20 mg at 2 years.

Table 4.11: The proportion of patients experiencing adverse events at a rate of ≥2% in the rimonabant group and ≥1% more than in the placebo group; results are pooled from 7 trials for the 1 year data (the 4 RIO Trials, REBA, EFC5745 and ACT3801) and 2 trials for the 2 year data (RIO-North America and RIO-Europe)

	Year 1		Year 2	
	Rimonabant (n=2742)	Placebo (n=2474)	Rimonabant (n=688)	Placebo (n=466)
Any event	86.3	81.4		
Nausea	13.6	4.7		
Diarrhoea	7.7	5.8		
Vomiting	4.7	2.3		
Dizziness	7.3	4.1		
Anxiety	5.9	2.1		
Insomnia	5.8	3.4		
Mood alterations with depressive symptoms	4.7	2.8		
Depressive disorders	3.9	1.7		
Influenza	10.3	9.1		
Asthenia/fatigue	6.1	4.4		
Gastroenteritis	4.5	3.5		
Contusion	3.1	1.1		
Hot flush	2.0	0.8		

There also seems to be some discrepancy in the reporting of adverse events between the clinical and cost-effectiveness sections of the submission. The clinical section states that 13 adverse events are associated with rimonabant at a rate of ≥2% in the rimonabant group and ≥1% more than in the placebo

group. These are: nausea; diarrhoea; vomiting; dizziness; anxiety; insomnia; mood alterations with depressive symptoms; depressive disorders; influenza; asthenia/fatigue; gastroenteritis; contusion, and hot flushes. In the cost-effectiveness section of the manufacturer's submission (Table 27), tendonitis is also identified as an adverse event, and influenza; asthenia/fatigue; gastroenteritis, and hot flushes are not included.

Furthermore, upper respiratory tract infection is considered very common (>10%) in the summary of product characteristics provided in the appendix of the original submission, but is not mentioned in the manufacturer's submission. Other adverse events listed as common (>1% and <10%) in the summary of product characteristics that were not mentioned in the submission include anxiety, irritability, nervousness, hypoaesthesia, sleep disorders, parasomnias, memory loss, sciatica, pruritus, hyperhidrosis, muscle cramp, and muscle spasms; given the lack of clarity regarding these events, it is unclear whether these were not mentioned as they occurred in <2% of patients prescribed rimonabant in the included trials. Some of the uncertainties surrounding adverse events related to rimonabant were clarified by the FDA report.[12]

A full review of the adverse events related to rimonabant was undertaken by the FDA advisory committee in June 2007.[12] The briefing document stated that 26.4% of patients prescribed 20mg of rimonabant in the RIO trials that withdrew in the first year, did so due to the occurrence of an adverse event, compared with 16.5% of those taking placebo. On p70 of the submission, the manufacturer highlights that there is a reduction in the number of adverse events in the second year, compared to the first, however, given the high dropout rates, these figures may be substantially underestimated. The manufacturer also states that the number of patients experiencing serious adverse events is similar between placebo and rimonabant ([redacted]), however, they do not define serious.

The committee identified the most significant adverse events as those in the primary System Organ Class (SOC) Psychiatric Disorders. These included

depressive events, psychomotor agitation, and sleep disorders. Overall, 26% of patients receiving 20mg rimonabant experienced some form of psychiatric adverse event across the four RIO trials, compared to 14% of patients receiving placebo. Symptoms of depression were reported in 9% of patients taking 20mg rimonabant compared to 5% of patients taking placebo. These rates were broken down further, with the most commonly reported psychiatric adverse events as stated in the FDA briefing presented in Table 4.12.

The overall risk of experiencing a psychiatric adverse event was significantly greater in patients prescribed rimonabant compared to placebo (RR 1.9; 95% CI: 1.5, 2.3). The proportion of patients requiring a prescription for an anxiolytic or hypnotic agent for a psychiatric adverse event was 8.5% for patients on 20mg rimonabant compared to 4.1% on placebo, and a further 4.8% of patients on 20mg rimonabant and 2.9% on placebo required a prescription for anti-depressants.

Table 4.12: The number (%) of patients experiencing psychiatric symptoms across the four RIO trials as reported in the FDA briefing document[12]

	20mg rimonabant	Placebo
Any psychiatric adverse event	569 (26.2)	226 (14.1)
Anxiety	131 (6.02)	40 (2.50)
Insomnia	118 (5.42)	53 (3.31)
Depressed mood	83 (3.81)	45 (2.81)
Depression	74 (3.40)	23 (1.44)
Irritability	1.93%	0.56%
Stress	38 (1.75)	28 (1.75)
Nervousness	31 (1.42)	5 (0.31)
Depressive symptom	23 (1.06)	12 (0.75)
Sleep disorder	21 (0.97)	7 (0.44)
Nightmare	21 (0.97)	3 (0.19)

The FDA committee expressed particular concern over the incidence of suicidality seemingly associated with rimonabant treatment. When the data from 13 studies (including those investigating alcohol and smoking cessation) were pooled, there was a significant increase in the rate of suicidality with 20mg rimonabant compared to placebo over the first year of treatment (RR 1.9; 95% CI: 1.1, 3.1). When the analysis was restricted to seven obesity

trials, the direction of effect was the same, but the pooled result was no longer significant (RR 1.8; 95% CI: 0.8, 3.8). However, this second analysis contained data for only 4681 patients, compared to 10,201 patients in the analysis of all 13 trials; the analysis of the obesity trials may have lacked the power to detect a difference for what is one of the rarer adverse events.

The FDA also summarised the incidence of neurological adverse event reported in the four RIO trials (Table 4.13). The overall risk of neurological adverse events was significantly higher with 20mg rimonabant compared to placebo (RR 1.7; 95% CI: 1.1, 2.7); the relative difference between rimonabant and placebo was greater in the RIO-Diabetes and RIO-Lipids studies compared to the RIO-Europe and RIO-North America studies.

Table 4.13: The number (%) of patients experiencing neurological symptoms across the four RIO trials as reported in the FDA briefing document[12]

	20mg rimonabant	Placebo
Any neurological adverse events	596 (27.4)	391 (24.4)
Dizziness	186 (8.55)	89 (5.56)
Headache	220 (10.11)	203 (12.67)
Parathesia	37 (1.70)	17 (1.06)
Migraine	36 (1.65)	31 (1.94)
Hypoaesthesia	31 (1.42)	14 (0.87)
Movement disorder	24 (1.10)	1 (0.06)
Peripheral neuropathies	21 (0.97)	19 (1.19)
Seizures	6 (0.3)	0

The FDA concluded that the incidence of suicidality, particularly suicidal ideation, and psychiatric and neurological adverse events were consistently higher for 20mg rimonabant compared to placebo.[12] As a result of this assessment, the FDA did not recommend the approval rimonabant for the treatment of overweight or obese patients in the USA.

Given this concern recently expressed over the psychiatric morbidity associated with rimonabant, particularly regarding depression and suicidality as highlighted by the FDA,[12] the safety profile of rimonabant was reviewed by the European Medicines Agency (EMEA).[13] The EMEA concluded that there

was an increased incidence of psychiatric morbidity with rimonabant that was dose dependent. However, the depressive disorders associated with rimonabant 20 mg were considered to be mild or moderate in severity, and most of the cases resolvable with corrective measures such as discontinuation of rimonabant or the use of anti-depressant treatment. In light of this, the licence for rimonabant was reviewed by the EMEA to preclude its use in patients with ongoing major depressive illness and/or ongoing antidepressive treatment.[14]

Although the licence has been revised, clinical advice to the ERG has highlighted that it is unrealistic to expect only those with a history of depression to experience psychiatric adverse events, given the pharmacological action of rimonabant. Given the adverse events associated with cannabis use, the long term use of rimonabant may not be considered safe without much better data. In addition, the cumulative data on less common side-effects is potentially important, and should be taken into consideration. In addition, there are a potentially large number of patients with depression and other psychiatric disorders that may remain undiagnosed at the time of commencing rimonabant treatment. The manufacturer states that there is no need for special monitoring of patients whilst being prescribed rimonabant (p3). However, monitoring for the presentation of symptoms of psychiatric illness, particularly during the early phases of treatment, may be needed, as many patients may not present to their doctors at the onset of symptoms.

4.3.3 Health-related quality of life

The manufacturer's assessment of HRQoL was based on the results of the RIO trials. They present the results of two tools: an obesity specific instrument (Impact of Weight on Quality of Life-Lite (IWQOL-Lite)) and the Medical Outcomes Study Short Form 36 (SF-36). A more detailed discussion of these HRQoL assessment tools is provided in Sections 5.3.4 and 5.4.5.

IWQOL-Lite

The differences between the rimonabant and placebo were statistically significant at 1 year in favour of rimonabant for:

- Physical function domain and IWQOL-Lite total score in all four RIO studies
- Self-esteem in RIO-North America, RIO-Diabetes and RIO-Lipids
- Public distress in RIO-Europe, RIO- North America and RIO-Lipids.
- Sexual life in RIO- North America and RIO-Lipids
- Work domains in RIO-Diabetes.

At 2 years (only available for RIO- Europe and RIO-North America), when patients remained on rimonabant for their second year rather than being re-randomised to placebo, differences between rimonabant and placebo were statistically significant in favour of rimonabant for:

- Physical function domain and IWQOL-Lite total score in the RIO-Europe trial
- Physical function domain, IWQOL-Lite total score and the self esteem domain in RIO-North America

When the results of the four RIO trials were pooled, differences between the rimonabant and placebo were [redacted] in favour of rimonabant, for all domains. There were no separate analyses of IWQOL-Lite data for diabetic and non-diabetic subgroups, as was conducted in the evaluation of clinical effectiveness of rimonabant.

SF-36

At one year, rimonabant was associated with a statistically significant improvement in the physical function domain in RIO-Europe, RIO-North America and RIO-Diabetes, and in the bodily pain and general health domains in RIO-North America. However, rimonabant was associated with a statistically significant deterioration in mental health in RIO-North America and RIO-Diabetes at 1 year.

When the 1 year data of the four RIO trials were pooled, differences between the rimonabant and placebo were [redacted] in favour of rimonabant, for the physical functioning, bodily pain, and general health domains. Differences in favour of placebo were seen in the role emotional and mental health domains. There were no separate analyses of SF36 data for diabetic and non-diabetic subgroups, as was conducted in the evaluation of clinical efficacy of rimonabant.

At 2 years, the only statistically significant result was an improvement in the physical function domain in RIO-Europe when the patients remained on rimonabant for the second year rather than being re-randomised to placebo.

The manufacturer stated that the lack of a statistically significant difference in some of the domains of the SF-36 form, and the general decline in scores over time compared to the general improvements seen in IWQOL-Lite scores was a result of the SF-36 tool failing to detect changes (p57). However, the SF-36 is a generic instrument which has been widely used in clinical trials and other research over a long period. An alternative interpretation of these results is that the clinical differences seen in trials had insufficient impact on patients HRQoL to register as significant treatment effects on the SF36. Furthermore, the SF-36 showed some significant differences at 1 year, but not all of these were in favour of rimonabant.

4.3.4 Comparison of rimonabant with orlistat and sibutramine

4.3.4.1 Effectiveness

To provide a complete overview of the efficacy and safety of rimonabant, an evaluation of its performance relative to that of the appropriate active comparators (orlistat/sibutramine) is essential. The results of the review of orlistat and sibutramine conducted by the manufacturer and included in their submission are presented in Table 4.14. No head-to-head comparisons of rimonabant compared to orlistat/sibutramine were identified, either by the manufacturer or the ERG. In their submission the manufacturer provided simple tabulated comparisons between the placebo-subtracted results for orlistat, sibutramine and rimonabant. The ERG considered this inadequate

and requested the results of a formal statistical analysis of the primary outcomes for the comparison between rimonabant and orlistat/sibutramine. Some pairwise comparisons were provided in the clarification submission and are given in Table 4.15 as presented by the manufacturer.

From the results of these formal pairwise comparisons, it can be seen that for most weight loss outcomes at one year, across the three patient populations specified, rimonabant was statistically significantly more effective than orlistat. The comparison with sibutramine found that the only significant difference between sibutramine and rimonabant was the number of patients achieving 5% weight loss at 1 year in the non-diabetic population in favour of rimonabant. Some results were not provided and, therefore, the relative effect of rimonabant to orlistat or sibutramine remains uncertain for these outcomes.

Table 4.14: Summary of results of review of efficacy of orlistat and sibutramine (table adapted from submission by ERG)

	Orlistat 360 mg + diet and exercise vs. placebo + diet and exercise Meta-analysis results using published data (fixed effects WMD [95% CI])			Sibutramine 10-15 mg + diet and exercise vs. placebo + diet and exercise Meta-analysis results using published data (fixed effects WMD [95% CI])		
	Subgroup equivalent to RIO-Diabetes	**Subgroup equivalent to RIO-Lipids**	**Subgroup equivalent to pooled data for non-diabetics**	**Subgroup equivalent to RIO-Lipids trial data**	**Subgroup equivalent to RIO-Diabetes trial data**	**Subgroup equivalent to pooled data for non-diabetics**
Change in weight (kg)	-2.53 [-2.97, -2.10]	-3.50 [-4.14, -2.85]	-2.75 [-3.03, -2.47]	-4.80 [-7.53, -2.07]	-4.12 [-6.18, -2.06]	-4.05 [-4.78, -3.32]
Change in BMI (kg/m^2)	-2.10 [-4.25, 0.05]	-	-0.93 [-1.53, -0.32]	-1.80 [-2.40, -1.20]	-1.10 [-2.26, 0.06]	-1.80 [-2.40, -1.20]
Change in waist circumference (cm)	-2.86 [-3.58, -2.14]	-1.50 [-2.86, -0.14]	-1.41 [-1.74, -1.08]	-5.0 [-6.73, -3.27]	-2.80 [-6.23, 0.63]	-3.69 [-4.53, -2.85]
Change in systolic blood pressure (mmHg)	-1.47 [-2.79, -0.15]	-2.39 [-3.95, -0.84]	-1.98 [-2.74, -1.21]	0.80 [-3.69, 5.29]	0.50 [-4.79, 5.79]	-0.34 [-3.46, 2.77]
Change in diastolic blood pressure (mmHg)	-	-	-	-	-	-
Change in total plasma cholesterol (mmol/L)	-0.32 [-0.39, -0.25]	-0.37 [-0.44, -0.31]	-0.39 [-0.47, -0.30]	0.01 [-0.19, 0.21]	-0.40 [-0.79, -0.01]	0.02 [-0.08, 0.12]
Change in LDL-C (mmol/L)	-0.25 [-0.32, -0.19]	-0.26 [-0.32, -0.20]	-0.27 [-0.34, -0.20]	-	-0.38 [-0.68, -0.08]	-0.03 [-0.13, 0.07]
Change in HDL-C (mmol/L)	-0.03 [-0.05, -0.02]	-0.02 [-0.04, 0.00]	-0.02 [-0.05, 0.01]	-	0.05 [-0.02, 0.12]	0.08 [0.04, 0.12]
Change in triglycerides (mmol/L)	-0.03 [-0.12, 0.06]	-0.08 [-0.18, 0.02]	0.01 [-0.13, 0.10]	-0.23 [-0.47, 0.01]	0.00 [-0.50, 0.50]	-0.17 [-0.28, -0.07]
Change in fasting plasma glucose (mmol/L)	-0.64 [-0.81, -0.47]	-0.12 [-0.20, -0.04]	-0.07 [-0.16, 0.01]	-0.03 [-0.49, 0.43]	-0.53 [-1.29, 0.23]	-0.03 [-0.49, 0.43]
Change in HbA_{1c} (%)	-0.29 [-0.37, -0.22]	-	-	-	-0.70 [-1.22, -0.18]	-

BMI, body mass index; HbA_{1c}, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol; RIO, Rimonabant in Obesity; WMD, weighted mean difference

Table 4.15: Pairwise comparisons for the primary outcomes between rimonabant and sibutramine, and rimonabant and orlistat, as presented in the manufacturer's resubmission; results in bold indicate *P*<0.05 for the indirect comparison of mean differences

Change in:	Rimonabant vs. Sibutramine			Rimonabant vs. Orlistat		
	RIO-Diabetes (or equivalent)	RIO-Lipids (or equivalent)	Non-diabetics	RIO-Diabetes (or equivalent)	RIO-Lipids (or equivalent)	Non-diabetics
Body weight (kg)						
Difference in the mean change from baseline vs. placebo [95% CI]	0.22 [-1.95, 2.39]	-0.60 [-3.46, 2.26]	-0.80 [-1.65, 0.05]	**-1.37 [-2.17, -0.57]**	**-1.90 [-2.96, -0.84]**	**-2.10 [-2.62, -1.58]**
Comparator (trials; total patients)	(2, 320)	(1, 324)	(4, 1438)	**(7, 2311)**	**(4, 1824)**	**(11, 7679)**
Rimonabant (trials; total patients)	(1, 681)	(1, 678)	(3, 3354)	**(1, 681)**	**(1, 678)**	**(3, 3354)**
Waist circumference (cm)						
Difference in the mean change from baseline vs. placebo [95% CI]	-0.50 [-4.04, 3.04]	0.30 [-1.67, 2.27]	-0.24 [-1.21, 0.73]	-0.44 [-1.57, 0.69]	**-3.20 [-4.85, -1.55]**	**-2.52 [-3.10, -1.94]**
Comparator (trials; total patients)	(1, 86)	(1, 324)	(3, 1278)	(6, 1651)	**(1, 479)**	**(2, 84)**
Rimonabant (trials; total patients)	(1, 680)	(1, 677)	(3, 3343)	(1, 680)	**(1, 677)**	**(3, 3343)**
BMI (kg/m^2)						
Difference in the mean change from baseline vs. placebo [95% CI]	-0.30 [-1.48, 0.88]	-0.20 [-0.87, 0.47]	0.04 [-0.58, 0.66]	0.70 [-1.46, 2.86]	Not provided	**-0.83 [-1.45, -0.21]**
Comparator (trials; total patients)	(1, 86)	(1, 324)	(1, 324)	(1, 108)		**(3, 190)**
Rimonabant (trials; total patients)	(1, 680)	(1, 677)	(3, 3353)	(1, 680)		**(3, 3353)**
Patients who achieved ≥5% body weight loss						
Relative risk [95% CI]	0.89 [0.49; 1.60]	Not provided	**1.30 [1.14; 1.48]**	**1.72 [1.27; 2.33]**	Not provided	**1.62 [1.51; 1.75]**
Comparator (trials; total patients)	(2, 217)		**(7, 2162)**	**(6, 2325)**		**(10, 7951)**
Rimonabant (trials; total patients)	(1, 681)		**(3, 3354)**	**(1, 681)**		**(3, 3354)**
Patients who achieved ≥10% body weight loss	0.99	Not	1.28	**3.67**	Not	**1.83**
Relative risk [95% CI]	[0.22; 4.42]	provided	[0.97; 1.70]	**[1.62; 8.33]**	provided	**[1.47; 2.27]**
Comparator (trials; total patients)	(2, 217)		(7, 2162)	**(5, 1956)**		**(8, 7185)**
Rimonabant (trials; total patients)	(1, 681)		(3, 3354)	**(1, 681)**		**(3, 3354)**

The ERG was unable to conduct their own systematic review of orlistat and sibutramine in order to check these results. As stated in Section 4.1.7.2, the selection of subgroups and trials for the review was difficult to follow and it is impossible to be confident that the correct data are being presented. The recent NICE guideline on the treatment of obesity included systematic reviews of orlistat and sibutramine and their findings are summarised below (Table 4.16).

Table 4.16: Summary data from NICE guideline (weighted mean difference compared with placebo plus diet (95% CI))[7]

	Orlistat + diet and exercise		Sibutramine + diet	
	All patients	**Diabetic patients**	**All patients**	**Diabetic patients**
Weight loss at 12 months (Kg)	-3.3 (-3.55, -3.00) (15 trials)	-2.68 (-3.18, -2.07) (3 trials)	-4.7 (-5.38, -4.03) (8 trials)	-5.69 (-6.84, -4.54) (3 trials)
Change in systolic blood pressure (mmHg)	-1.98 (-2.54, -1.42) (13 trials)	-1.62 (-2.99, -0.25) (3 trials)	1.36 (-0.14, 2.86) (7 trials)	0.91 (-1.88, 3.7) (3 trials)
Change in diastolic blood pressure (mmHg)	-1.42 (-1.80, -1.05) (12 trials)	-1.28 (-2.40, -0.52) (2 trials)	2.16 (1.20, 3.11) (7 trials)	1.6 (-0.05, 3.35) (3 trials)
Change in total plasma cholesterol (mmol/L)	-0.36 (-0.40, -0.31) (12 trials)	-0.40 (-0.50, -0.30) (3 trials)	0.03 (-0.11, 0.18) (6 trials)	0.15 (-0.17, 0.47) (2 trials)
Change in LDL-C (mmol/L)	-0.30 (-0.33, -0.27) (12 trials)	-0.28 (-0.35, -0.20) (3 trials)	-0.03 (-0.14, 0.07) (5 trials)	0.05 (-0.17, 0.27) (2 trials)
Change in HDL-C (mmol/L)	-0.04 (-0.05, -0.03) (10 trials)	-0.01 (-0.04, 0.02) (3 trials)	0.10 (0.06, 0.14) (5 trials)	0.10 (0.01, 0.19) (2 trials)
Change in triglycerides (mmol/L)	-0.01 (-0.06, +0.03) (10 trials)	-0.22 (-0.32, -0.12) (3 trials)	-0.18 (-0.28, -0.08) (7 trials)	-0.30 (0.89, -0.01) (2 trials)
Change in fasting plasma glucose (mmol/L)	-0.24 (-0.31, -0.18) (10 trials)	-0.84 (-1.04, -0.64) (3 trials)	-0.15 (-0.35, 0.06) (5 trials)	-0.40 (-0.81, 0.00) (2 trials)
Change in HbA_{1c} (%)	-0.23 (-0.28, -0.17) (6 trials)	-0.36 (-0.45, -0.28) (3 trials)	-0.21 (0.80, 0.37) (2 trials)	-0.21 (-0.80, 0.37) (2 trials)

The results derived from the small number of trials selected to fit the base cases and sensitivity analyses in the manufacturer's submission are similar to those presented in the NICE guidelines, although the weight loss achieved, particularly in diabetic patients treated with sibutramine, may be understated in the submission.

The ERG notes some examples of response curves of orlistat and sibutramine in the literature (these were not systematically searched for). The response curve of rimonabant presented by the manufacturer (Figure 4.3) shows a

progressive weight loss over the first 8 months, with patients achieving between an 8 to 10 kg weight loss (although the reported value is 6.3 kg in Table 4.3); which levels off in patients who continue to receive rimonabant during year 2 of the trial. Similar response curves have been reported for orlistat.[19, 20] The response curve identified for sibutramine showed a more rapid weight loss, with maximum weight loss being achieved by 3 months.[21]

When comparing rimonabant with orlistat and sibutramine, the manufacturer only made a comparison of 1 year data. A comparison between rimonabant and sibutramine beyond this time period would not be expected, given the restriction to treatment for 1 year with sibutramine (see Section 3.3). However, trials evaluating the effectiveness of orlistat beyond 1 year are available. When a comparison of two year data between rimonabant and orlistat was requested, the manufacturer stated that the trials were not comparable, as patients in the orlistat trials tended to be placed on a maintenance diet for the second year, rather than the hypocaloric diet as in the RIO trials of rimonabant.

The ERG undertook a brief comparison of the dietary regimes between the RIO trials and some of the orlistat trials for which 2-year data was available. The hypocaloric diet imposed in the RIO trials was a 600 kcal deficit from their usual intake. When considering the dietary regimen of four of the orlistat trials that presented 2-year data,[22-25] two prescribed a 600 kcal deficit from the patients usual intake,[22, 24] one prescribed a deficit of between 500 and 800kcal,[25] and the fourth prescribed a diet of1200-1500kcal daily intake, rather than imposing a deficit.[23] In the second year, two trials recommended an increase in calorie intake of 200-300kcal,[23, 25] and two prescribed a calorie intake of their daily expenditure minus 10%;[22, 24] both of these were only applied to patients still losing weight at the end of the first year. Given that the dietary regimen of two of the orlistat trials does not appear to be comparable to the RIO trials in the first year, and the changes in calorie intake were potentially relatively small and only imposed in a proportion of the participants, the ERG does not believe that the response by the manufacturer is adequate justification for not undertaking the comparison.

4.3.4.2 Adverse events

There was no comparison of adverse events or between rimonabant and orlistat or sibutramine. A full comparison of adverse events between rimonabant and orlistat and sibutramine was requested by the ERG, but not provided.

4.3.4.3 HRQoL

There was no comparison of HRQoL between rimonabant and orlistat or sibutramine.

4.3.5 Generalisability of results

The company submission was based primarily on the four RIO trials. Only one of these trials included people from the UK. Furthermore, not only did this single trial with UK patients include patients from 11 other countries, it was also the trial of the diabetic subgroup. Given the differences in lifestyle, diet and attitudes towards alcohol consumption and exercise between the UK and the USA and other European countries, generalisability to the overweight/obese UK population is uncertain. In addition, the main included study of diabetic patients, RIO-Diabetes, permitted only metformin and sulphonylureas as antidiabetic medication. This clearly excludes those patients who require insulin therapy, and the efficacy of rimonabant in this population is unknown.

The manufacturer states that the majority of prescriptions (87%; p1) are administered to patients in the >27 BMI category who have comorbidities, with only 12% of prescriptions administered to patients with a BMI>30 without other risk factors. The proportion of patients in each BMI category who received rimonabant was not provided, nor was the proportion of patients in the RIO trials that had different types of comorbidity. However, a recent EMEA document[13] provided an insight into these data. The EMEA stated that:

- Approximately 55-60% of the included patients had dyslipidaemia at baseline in the different studies (100% in the RIO-lipids)

- The prevalence of hypertension was between 27 and 61 %, with the highest prevalence in the RIO-diabetes study
- The number of patients treated for hypertension varied from 55% in RIO-Europe to 93% in RIO diabetes and was approximately 68% in the RIO-North America and RIO-Lipids studies
- Overall, 46.5% of the patients included in the RIO studies had metabolic syndrome with a prevalence of 35, 41, 54 and 79% in the RIO-North America, RIO-Europe, RIO-Lipids and RIO-Diabetes, respectively

Therefore, the overall proportion of patients with comorbidities in the RIO trials seems representative of the population being prescribed rimonabant in practice.

When the data from the trials were analysed separately stratified by baseline BMI it was not apparent that the difference seen between rimonabant and placebo were being driven by any one BMI group. However, the numbers of patients included in some of these analyses was very low (particularly for the >40 category in the RIO-Lipids trial), reducing their power to detect differences. There was no stratified analysis of pooled data from the three RIO trials providing data for the non-diabetic population. If a stratified analysis were conducted on the pooled data for the non-diabetic population, the number of patients included in each BMI category in the analysis would have been substantially increased, increasing their power to detect differences.

4.3.6 Placebo response

Clinical advice suggests that the efficacy of rimonabant expressed as the difference compared to placebo must be interpreted carefully, and that the placebo responses in the RIO trials seem rather low in comparison to some published trials of lifestyle and dietary changes. To put into context the placebo responses seen in the rimonabant, orlistat and sibutramine trials, the ERG looked at results achieved in trials of diet and/or exercise compared to no treatment as summarised in the NICE guidelines (Table 4.17),[7] and also results of the Look Ahead trial.[26-28] The Look Ahead study,[26, 27, 29] investigating life-style changes in diabetic patients, showed patients with type 2 diabetes achieving nearly a 8% greater mean reduction in body weight

compared to patients that did not undergo life-style changes, accompanied by a nearly 6 cm mean reduction in waist circumference. These results would suggest that the weight loss achieved by the placebo arm in the rimonabant trials is below that which can be achieved with diet and exercise. This does not necessarily impact on the generalisability of the relative effect of rimonabant reported from the trials.

Table 4.17: Results achieved in trials of diet and exercise (or just diet) compared to no treatment as summarised in the NICE guidelines[7]

	600Kcal deficit or low fat diet	Physical activity (minimum 30 mins3x per week)	Physical activity (minimum 45 mins3x per week)and Diet
Weight loss (WMD; 95% CI) at 12 months	-5.32 (-5.88, -4.75) (12 trials)	-3.09 (-4.00, -2.18) (3 trials)	-6.87 (-7.88, - 5.87) (3 trials)
Change in systolic blood pressure (mmHg)	-3.38 (-5.53, -2.03) (4 trials)	-2.13 (-4.83, (0.56) (2 trials)	-4.60 (6.61, -2.58) (3 trials)
Change in diastolic blood pressure (mmHg)	-3.44 (-4.86, -2.01) (4 trials)	-1.78 (-4.18, 0.62) (2 trials)	-4.64 (-6.04, -3.25) (3 trials)
Change in total plasma cholesterol (mmol/L)	- 0.21 (-0.34, -0.08) (4 trials)	0.03 (-0.21, 0.15) (2 trials)	-0.27 (-0.42, -0.12) (3 trials)
Change in LDL-C (mmol/L)	-0.13 (-0.26, 0.00) (4 trials)	0.04 (-0.13, 0.21) (2 trials)	-0.20 (-0.33, -0.06) (3 trials)
Change in HDL-C (mmol/L)	0.06 (0.03, 0.09) (4 trials)	0.07 (0.03, 0.11) (2 trials)	0.12 (0.09, 0.13) (3 trials)
Change in triglycerides (mmol/L)	-0.19 (-0.31, -0.06) (4 trials)	-0.03 (-0.49, -0.10) (2 trials)	-0.29 (-0.41, -0.17) (3 trials)
Change in fasting plasma glucose (mmol/L)	-0.28 (-0.47, -0.09) (1 trial)	-0.0.16 (-34, 0.02) (1 trial)	-0.33 (-0.54-0.12) (3 trials)

4.3.7 Summary

The key issues highlighted in the ERG report are:

- The effects of rimonabant on weight loss and related outcomes and outcomes related to cardiovascular risk factors are significantly better than placebo
- For any baseline BMI, the average weight loss beyond that which can be achieved with diet and exercise over a one year period is [redacted] with a [redacted] BMI of [redacted].

- Rimonabant provided benefits in some areas of HRQoL, particularly the physical function domain
- There was a significant deterioration in mental health associated with rimonabant.
- There is a lack of longer-term data; there is no effectiveness or safety data presented for rimonabant beyond 2 years, and data available beyond 1 year is limited.
- Data for year 2 is less favourable than that for year 1, and it is unclear whether this trend would continue; as treatment would need to be continued to maintain weight loss, the lack of long-term data is cause for concern.
- There is no evidence for the effect of rimonabant on hard outcomes, such as cardiovascular events and mortality.
- Data for surrogate outcomes provide no indication that rimonabant had any adverse effect on cardiovascular risk factors compared to placebo.
- Comparison of the effects of rimonabant on weight loss outcomes with those of orlistat and sibutramine suggest that rimonabant is significantly more effective than orlistat but not sibutramine
- Apart from an increase in blood pressure in the lipid and diabetic subgroups with sibutramine, there seems little difference between rimonabant and orlistat and sibutramine in terms of their effects on cardiovascular risk factors.
- There was no comparison of 2 year data between rimonabant and orlistat
- Overall, the ERG found the presentation of the data unclear, particularly that for orlistat and sibutramine.
- The ERG has doubts over how representative of the general literature the trials of orlistat and sibutramine included in the submission are, and how objectively the data have been used.
- There are differences in the licence of rimonabant compared to orlistat and sibutramine; orlistat and sibutramine are subject to response hurdles in practice that may not be applied in trials, therefore any additional benefit of rimonabant over orlistat or sibutramine may be overestimated, and may not be apparent in normal clinical practice.

5 ECONOMIC EVALUATION

5.1 Introduction

This section provides a structured critique of the cost-effectiveness model submitted by the manufacturer (the manufacturer). As part of the STA process, manufacturers are expected to perform a systematic review of existing cost-effectiveness evidence for the health care technology or process being assessed. Where there is no existing evidence or the existing evidence is insufficient, manufacturers may perform their own *de-novo* cost-effectiveness analysis.

The manufacturer's economic submission to NICE includes:

(i) a description of the systematic search undertaken in an attempt to identify relevant cost-effectiveness studies of rimonabant, orlistat and sibutramine (p111-113; Appendix 7 of the manufacturer's appendices);

(ii) a report on the economic evaluation undertaken by the manufacturer (p75-129 in the manufacturer's submission, in particular Figure 13, p81 the schematic of the model and Tables 25 - 39, p81-102 which provide information on the model input parameters and assumptions);

(iii) base-case cost-effectiveness results from the model (Tables 42 - 47, p109-116);

(iv) subgroup cost-effectiveness results from the model (Table 48, p116-117);

(v) results from the deterministic one-way sensitivity analyses conducted (Tables 49 - 51, p117-122);

(vi) results from the probabilistic sensitivity analysis conducted (Figures 14 - 19, p122-126);

(vii) an Excel-based model comprising the manufacturer's economic model provided electronically; and

(viii) a report on the discrete event simulation (DES) economic evaluation (Appendix 9.12).

Following a number of points of clarification raised by the ERG to the manufacturer, a number of addenda were submitted by the manufacturer. These include:

(i) a full technical report for the Markov model (SHAPE Technical Report 12-09-07a Final.doc);

(ii) further clarification on specific issues related to the economic model and the results of additional analyses requested by the ERG in relation to providing a simultaneous comparison of all treatments and a comparison of the cost-effectiveness of rimonabant incorporating response hurdles based on weight loss targets (Final response to clarification queries 14 09 07.doc).

This section focuses on the economic evidence submitted by the manufacturer. The submission is subject to a critical review on the basis of the manufacturer's report and by direct examination of the electronic version of the economic model. The critical appraisal is conducted with the aid of a checklist to assess the quality of economic evaluations and a narrative review to highlight key assumptions and possible limitations. These areas are then used to formulate the points for clarification raised by the ERG to the manufacturer. Section 6 presents a description of the additional analyses requested from the manufacturer and a critique of their re-submitted results, alongside additional work undertaken by the ERG to address any remaining uncertainties.

5.2 Existing cost-effectiveness evidence

As part of the manufacturer's submission a systematic search was undertaken with the aim of identifying all studies evaluating the cost-effectiveness of rimonabant, orlistat and sibutramine for the treatment of obesity. No studies of the cost-effectiveness of rimonabant were identified by the manufacturer as part of this search. However, one study by Caro et al (2007),[30] which appears to have been published after the search was undertaken, was reported by the manufacturer. The details of the search are provided in Appendix 7 of the manufacturer's submission. The search strategy was critically appraised by an experienced information scientist within the ERG.

Although the manufacturer undertook a search of most of the required databases for studies of the cost-effectiveness, a search of the Cochrane Library was not conducted. However, searches of additional relevant databases were undertaken: including NHS EED, HEED and Biosis. The focus of the search reported in the appendix (rimonabant) is different from the stated purpose in the body of the report: 'relevant studies of the cost-effectiveness of rimonabant, orlistat and sibutramine' (p.75). The search strategy as reported will only retrieve records about orlistat or sibutramine where those drugs feature in comparisons to rimonabant.

A MEDLINE search strategy only is reported. The database searches were reported to have been run on Datastarweb. However, the search syntax reported is not correct for Datastarweb. The ERG was therefore unable to rerun the strategy as presented in the PubMed, Datastarweb or Ovid interfaces to MEDLINE. In addition, the ERG was unable to verify how the strategy was adapted for databases other than MEDLINE. However, the structure of the search strategy as reported was considered suitable for capturing rimonabant cost-effectiveness studies in MEDLINE. In addition, the words used in the strategy are adequate to capture the topic. Sensitivity might have been enhanced by the use of additional quality of life terms, such as "quality-adjusted" "qalys" etc.

Although unable to re-run the searches as reported in the submission, the ERG translated the strategy generously (assuming broad searches of all fields for terms that were not subject headings) and ran it in MEDLINE (1950 to 28 Sept 2007) on Datastarweb. The translated search yielded 10 records. The strategies used with the other databases were not reported so it was not possible to replicate or translate them. No additional studies relating to the cost-effectiveness were identified using the translated search.

This study by Caro et al (2007)[30] mentioned in the manufacturer's submission evaluated the cost-effectiveness of rimonabant compared to diet and exercise from a UK NHS perspective. This study is based on the same model used as

part of the manufacturer's own submission and hence is not considered in any more detail by the ERG.

5.3 Overview of manufacturer's economic evaluation

The manufacturer's submission evaluates the cost-effectiveness of rimonabant (20 mg once daily), as an adjunct to diet and exercise, for the treatment of obesity (BMI ≥30 kg/m^2), and overweight patients (BMI ≥27 kg/m^2) with associated risk factors. Rimonabant is compared with orlistat (120 mg tid or with each meal), sibutramine (10-15 mg per day) and non-pharmacological (diet and exercise alone) therapies. A brief overview of the key assumptions used in the analysis, alongside a narrative description of the main approach used, is reported below. This is followed by a more detailed critique of the economic evaluation and its assumptions.

The key assumptions applied in the model include:

(i) Treatment with rimonabant and orlistat is continued over a lifetime duration (60 years), while treatment with sibutramine is continued for 1 year in accordance with its licence. Treatment with all of the anti-obesity drugs is assumed to continue regardless of whether patients have achieved a specific target weight loss at a pre-determined time point (e.g. 5% at 3 months).

(ii) The lag until the full treatment effect is reached is assumed to be 9 months for all treatments (sensitivity analyses employing shorter treatment lags for orlistat and sibutramine are also conducted). The clinical benefits achieved in the first year are maintained at this level for the duration of treatment, but lead to no further reduction in weight or improvement in other risk factors. Where treatment is discontinued, the effects reduce linearly over a further 12 months.

(iii) Changes in established risk factors, resulting from treatment, are assumed to translate to a reduced risk of cardiovascular disease (CVD), and in patients without diabetes, to a reduced risk of developing diabetes. Once patients develop CVD or diabetes they are assumed to receive standard therapy, independent of any weight loss treatments that they may have been receiving.

Treatment with the anti-obesity drugs is assumed to be discontinued after an initial CVD event. Hence, the risk of a subsequent CVD event and death is assumed to be independent of the initial anti-obesity treatment received.

(iv) The risk factors considered include: BMI, body weight, systolic blood pressure (SBP), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides, fasting plasma glucose (FPG) and, in patients with diabetes, HbA_{1c}. Pooled patient-level data from the RIO-trials are used to inform changes in these risk factors when treated with diet and exercise alone or rimonabant adjunctive to diet and exercise. A meta-analysis of clinical trial results for orlistat and sibutramine is used to estimate changes in patients' associated cardiovascular risk factors for these treatments.

(v) BMI is assumed to independently influence health-related quality of life beyond that attributed to the effect on CVD and diabetes risks. A one unit reduction in BMI is assumed to be associated with an additional 0.014 increase in utility.

(vi) Adverse event rates for orlistat and sibutramine are assumed to be the same as diet and exercise alone. For all comparators, adverse events are only included in terms of their costs. No negative effects on health utilities are assigned.

(vii) Death due to causes other than CVD is assumed to be independent of the anti-obesity treatments.

The results of the economic evaluation are presented for 3 base-case populations, comprising:

- Overweight or obese patients with treated type 2 diabetes (diabetic group)
- Overweight or obese patients with dyslipidaemia (defined as triglycerides > 1.7 mmol/L or total plasma cholesterol > 5.0 mmol/L or LDL-C > 3.0 mmol/L or HDL-C <1.03 mmol/L for men, and triglycerides > 1.7 mmol/L or total plasma cholesterol > 5.0 mmol/L or LDL-C > 3.0

mmol/L or HDL-C <1.29 mmol/L for females) not treated with a statin, and without type 2 diabetes (dyslipidaemic group)

- Obese patients with or without comorbidities (obese group). This group is subdivided into (i) patients with diabetes and (ii) patients without diabetes.
-

In addition, separate sensitivity analyses are conducted in specific subgroups. These include:

- BMI > 27 kg/m^2 with diabetes or dyslipidaemia, or BMI ≥ 30 kg/m^2
- BMI > 27 kg/m^2 being treated with a statin, but without diabetes
- BMI ≥ 30 kg/m^2 with treated type 2 diabetes
- BMI > 27 kg/m^2 with treated type 2 diabetes and a baseline HbA_{1c} <7%
- BMI > 27 kg/m^2 with treated type 2 diabetes and a baseline HbA_{1c} ≥7%
- BMI > 27 kg/m^2 with treated type 2 diabetes and a baseline HbA_{1c} ≥8%
- BMI ≥ 30 kg/m^2 with dyslipidaemia, not treated with a statin, and without type 2 diabetes.

Deterministic sensitivity analyses are undertaken on a range of parameters and assumptions. Probabilistic sensitivity analysis (PSA) is also undertaken. Table 5.1 provides a summary of the structure, assumptions and evidence sources used for the manufacturer's economic evaluation.

Table 5.1: Summary of manufacturer's economic evaluation

	Assumption	Source/justification	Signpost‡
Model	Markov state-transition model with lifetime horizon, cycle length of 1 month.	Allows changes in CVD and diabetes risks to be modelled over time.	Section 6.2.6 (pg 79). Figure 13 (pg 81).
Comparators	Lifetime treatment duration for rimonabant, orlistat and diet and exercise. 1-year treatment duration for sibutramine. Treatment assumed to continue regardless of achievement of specific weight loss target.	Manufacturer recommends maintenance of treatment over the longer term. Treatment with sibutramine restricted to 1 year due to its licence. No justification provided for continuing treatment if a target weight loss has not been achieved.	Section 3 (pg 9-10).
Subgroups	Base-case and subgroup populations match RIO trial populations.	Consistent with the scope of the decision problem.	Section 6.2.2 (pg 76).
Natural history	Changes in risk factors resulting from treatment translate to a reduced risk of CVD and/or diabetes. Onset of an event results in treatment discontinuation. Risk of subsequent events is independent of treatment.	No direct evidence available to quantify the impact of treatment on the risk of CVD and/or diabetes. A series of published risk equations provided an indirect link.	Section 6.2.6 (pg 85).
Treatment effectiveness	RIO trials used solely to synthesis treatment effectiveness evidence for rimonabant and diet and exercise. Indirect comparison methods used to establish the relative effectiveness of orlistat and sibutramine. Treatment effects at 1-year maintained for the duration of treatment (lifetime for rimonabant and orlistat).	A systematic review of the literature identified the RIO trials as matching the manufacturer's inclusion and exclusion criteria. No direct head-to-head RCT data available to compare rimonabant with the active comparators. No justification provided for the method of indirect comparison used. Maintenance of benefits beyond 1-year based on observed outcomes in the RIO trials at 2 years.	Section 5 (pg 20 - 29). Section 5.6 (pg 62). Section 6.2.7 (pg 94-98). Section 5.4 (pg 47).
Transition probabilities	Surrogate endpoints based on changes in risk factors were applied to external published risk equations and other epidemiological data in order to extrapolate over a lifetime time horizon.	San Antonio Heart Study.[31] Framingham Heart Study with Mora adjustment.[32, 33] UKPDS 68.[34] No justification provided for the rationale for selecting these equations.	Section 6.2.7 (pg 90).
Health-related quality of life	BMI assumed to independently influence health-related quality of life. External utility estimates assigned to BMI change and the main health states.	HODaR.[35] No additional supportive evidence provided.	Section 6.2.8 (pg 99). Table 29 (pg 85)
Adverse events	Only considers the costs of managing adverse events. Adverse event rates for orlistat and sibutramine assumed the same as diet and exercise.	No justification provided for not assigning utility decrements to adverse events. Manufacturer states belief that adverse events rates for comparator treatments is conservative.	Section 6.2.9 (pg 102). Table 28 (pg 84).
Resource utilitisation and costs	Treatment costs include drug acquisition and monitoring costs based on frequency of GP and nurse visits per year. Drug compliance rates for orlistat and sibutramine assumed the same as reported in RIO trials.	Limited justification provided for the monitoring costs. No justification provided for drug compliance rates for comparator drugs.	Section 6.2.9 (pg 101). Table 39 (pg 102). Table 28 (pg 84).
Discount rates	3.5% for health outcomes and costs	In accordance with NICE guidance.[36]	

‡Refers to manufacturer's submission

5.3.1 Natural history

Two economic evaluations are conducted by the manufacturer: a cohort Markov model and an individual patient discrete event simulation (DES). The manufacturer's economic submission to NICE includes the Markov model, while results for the DES are also presented for comparative purposes. This report focuses on the Markov model.

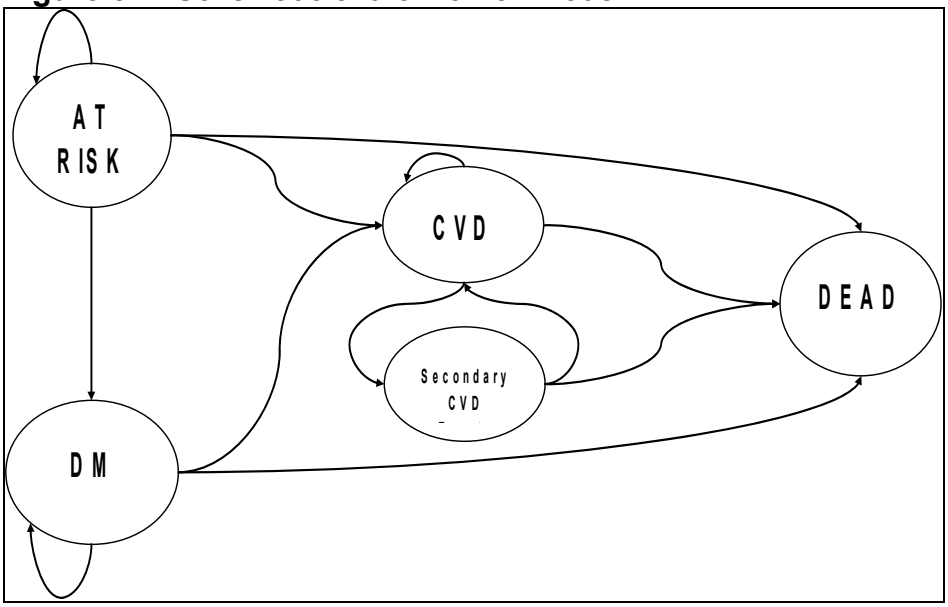
The Markov model describes the natural history of obesity by modelling separate patient cohorts from time of entry into the model until death (i.e. lifetime horizon). For each patient cohort, representing a particular subgroup, the model predicts the long-term impact of obesity on the development of diabetes and CVD, and assesses the benefit of treatment on these outcomes. Quality of life benefits are also assumed to be conferred directly via a reduction in BMI which is considered to be independent of the impact of BMI on diabetes and CVD events.

The main model is a Markov state-transition process where the cohort population can be in any one of four main states: (1) AT RISK (non-diabetic and no CVD); (2) DM (diabetic and no CVD); (3) CVD; and (4) DEAD. In addition, the CVD state incorporates a collection of substates representing separate events, namely, MI, ANGINA, STROKE, and TIA.

The patient cohort starts in either the AT RISK or DM state, depending on their diabetes status. The mean risk profile of the cohort determines the subsequent risks of CVD events and diabetes. Patients starting from AT RISK can move to any one of the three other states, while patients starting from DM can move to CVD or DEAD. The risk of transition to CVD is calculated separately for men and women based on baseline risk profiles, effects of treatment and ageing of the cohort over time. Transitions from CVD back to AT RISK or DM are excluded. Subsequent CVD events, recording secondary CVD events, are possible within the CVD state in a given cycle. Transitions from CVD to DEAD incorporate two types of death: within-case fatality applied to acute events, and subsequent deaths resulting from the

increased risk of death from chronic CVD. Transitions from AT RISK and DM to DEAD reflect deaths due to causes other than CVD. The cycle length is one month. A schematic of the model is presented in Figure 5.1.

Figure 5.1: Schematic of the Markov model



5.3.2 Treatment effectiveness

The clinical data used in the economic evaluation for the comparison of rimonabant with placebo as an adjunct to diet and exercise is from the RIO trials that formed part of the RIO programme. The principal subgroups of the analyses are chosen to match the design of the specific trials. For example, RIO-Diabetes and RIO-Lipids, which recruited patients with treated type II diabetes and untreated dyslipidaemia, respectively, are used to inform the treatment effectiveness of the subgroups corresponding to these conditions. For other defined subgroups, the effects of treatment are derived using pooled patient-level data from all the RIO trials within the programme.

Given the lack of head-to-head trials comparing rimonabant with orlistat and sibutramine, an indirect comparison is used to obtain effectiveness inputs for orlistat and sibutramine. Relevant studies were identified through a systematic review of the literature comparing the active comparators with placebo as an adjunct to diet and exercise. Where data were available, it

was pooled in a meta-analysis and used to determine the effects of orlistat and sibutramine on BMI and associated risk factors. In order to allow for meaningful comparisons with the rimonabant data, the estimates for orlistat and sibutramine were adjusted so that all comparators referred to the same baseline. This was achieved by adding the difference between the active comparator and the placebo to the difference between the placebo and the baseline results from the RIO trials. Hence, treatment effects for all comparators are assessed as the mean change in individual risk factors compared to a common baseline (representing the mean risk profile of the separate cohorts prior to treatment).

The approach is illustrated with a worked example presented by the manufacturer and replicated in Table 5.2. Separate treatment effects are estimated for the different subgroups; studies of orlistat and sibutramine were categorised and then pooled in relation to the different subgroups outlined by the manufacturer. The treatment effects are applied for the intended duration of the treatment and the time period over which the effects waned after treatment is stopped. Once patients entered the CVD state, the treatment with the anti-obesity drugs is terminated.

Table 5.2: Adjusting published orlistat data for indirect comparison: a worked example

	RIO Trial data			**Meta-analysis of Orlistat data**	**Adjusted Orlistat**
	Rim	Plbo	Δ R vs. P	Δ O vs. P	
E.g.	R	P_R	$R - P_R$	$O - P_O$	$P_R + (O - P_O)$
Weight	–5.3	–1.4	–3.9	–2.53	–3.93

Changes in patients' BMI, weight, HDL-C, LDL-C, total plasma cholesterol, systolic blood pressure, fasting blood glucose and HbA_{1c} are estimated for each treatment using the aforementioned approach. These are then applied to the mean risk profiles of the modelled population. The baseline risk-factor profile for the starting states of AT RISK and DM are determined from the three RIO trials and RIO-Diabetes, respectively. Separate risk-factor profiles

are used for males and females. In order to increase the generalisability of the economic evaluation to the UK population, baseline characteristics of individuals who matched the profiles from the RIO trials were extracted from the Health Survey of England database[37] and the treatment effectiveness data applied to the corresponding risk profiles of the appropriate patient subgroup. Tables 5.3 and 5.4 report the baseline characteristics of the main populations applied in the model.

Table 5.3: Baseline characteristics of the primary simulated populations with diabetes[37]

	BMI >27 kg/m^2 with diabetes	**BMI ≥30 kg/m^2 with diabetes**
Age (years)	60.5	58.6
Male (%)	55.7	54.1
BMI kg/m^2	32.8	35.2
SBP (mmHg)	137.1	137.9
Total plasma cholesterol (mmol/L)	5.7	5.6
HDL-C (mmol/L)	1.3	1.2
LDL-C (mmol/L)	3.5	3.4
Triglycerides (mmol/L)	2.4	2.5
HbA_{1c}	7.6	7.6
Smoker (%)	15.7	16.2

BMI: Body mass index; HbA_{1c}: glycosylated haemoglobin; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; SBP: systolic blood pressure

Table 5.4: Baseline characteristics of the primary simulated populations without diabetes[37]

	BMI >27 kg/m^2 with untreated dyslipidaemia	**BMI ≥30 kg/m^2**
Age (years)	49.3	49.0
Male (%)	49.3	44.6
BMI (kg/m^2)	31.3	34.0
SBP (mmHg)	132.2	133.0
Total plasma cholesterol (mmol/L)	6.0	6.0
HDL-C (mmol/L)	1.4	1.4
LDL-C (mmol/L)	3.6	3.6
Triglycerides (mmol/L)	1.8	1.9
Fasting glucose (mmol/L)	5.1	5.2
Family history of diabetes	17.4	17.1
Smoker (%)	21.9	21.0

5.3.3 Transition probabilities

In the absence of long-term trials evaluating the effect of rimonabant on 'hard' clinical endpoints such as mortality, diabetes and CVD events, surrogate outcomes based on changes in risk factors are applied to published risk equations and other epidemiological data in order to extrapolate the model over a lifetime time horizon. Hence, a central component of the manufacturer's submission is the set of risk equations that translate the patient's risk factor profile to the probability of transition to one of the other states. Published risk equations and epidemiological data are utilised and re-parameterised to calculate monthly transition probabilities for the model. The main risk equations are reported to be based on well established and validated risk equations. These covered the following sets of transitions:

AT RISK to CVD

For patients in the AT RISK (no diabetes and no CVD) health state, the transition probability to CVD is based on the 1990 Framingham Heart Study (FHS) published risk equations that predict first cardiovascular events.[32] The hazard of CVD and stroke is derived as a function of age, gender, SBP, smoker status, and total cholesterol to high-density lipoprotein ratio (TC:HDL). As the original 1990 FHS does not include BMI, the additional effect of BMI on CVD risk is incorporated using the hazard ratio reported by Mora et al[33] based on a sample of 827 subjects from the John Hopkins Sibling Study. For each unit increase in BMI, the CVD risk increases 3.77% beyond the Framingham risk prediction score. This is incorporated into the equation for the monthly transition probability by adjusting the hazard rate estimated from the FHS.

DM to CVD

For patients with diabetes (no CVD), the risk of CVD is determined by the published risk equations from the UK Prospective Diabetes Study (UKPDS 68).[34] A single equation predicting CVD from the UKPDS has not been published; instead separate equations are estimated for the hazard of a MI, ischaemic heart disease (IHD, angina), stroke and CHF following diagnosis of type II diabetes. The risk of CVD is then implemented in the model by summing the individual hazards of MI, IHD and stroke.

AT RISK to DM

The probability of developing diabetes in the cohort initially without diabetes is estimated using the logistic risk equation from the San Antonio Heart Study.[31]

Subsequent CVD events

Following an initial non-fatal CVD event (MI, angina, stroke or TIA), the risk of a subsequent event of MI or stroke is included in the manufacturer's submission. Data from the Saskatchewan Health database is used to derive the hazards for a subsequent event.[38-40] The specific data used to inform the risk include individuals over the age of 21 who suffered an MI (ICD-9 code 410) or an ischaemic stroke (ICD-9 codes 433, 434, 436, 362.3) between the start of January 1990 and the end of December 1995. The data were followed through to December 2002. The event-free time was measured from the date of the index event to the date of a subsequent event, and standard Kaplan-Meier methods used to estimate event-free survival. Daily hazards were estimated according to patient characteristics, separately for diabetic and non-diabetic individuals at the time of the index MI or stroke. These hazards are converted to monthly probabilities for the model. It is assumed that the risks of post-events (MI or stroke) following angina and TIA are the same as those following MI and stroke, respectively.

DEAD

The dead state incorporates death due to CVD events and other cause mortality. The monthly transition probabilities from the two pre-cardiovascular disease states are derived from Gompertz functions based on UK lifetable data for the general population with CVD deaths subtracted.[41] Death from the CVD state incorporates within-case fatality applied to acute events and deaths due to chronic CVD. A proportion of the cohort that transferred from the two pre-cardiovascular disease states to CVD is assumed to suffer an acute fatality. These case fatality rates are derived from the Saskatchewan Health data[38-40, 42-44] for hospitalised patients by calculating an average hazard based on deaths occurring within one month of the index event. The proportion of cases dying before hospitalisation for MI and stroke are estimated from alternative data sources (see pg93 of the manufacturer's submission for

references). It is assumed that there were no cases of dying before hospitalisation for angina or TIA. Death due to chronic CVD occurred in subsequent cycles of the model with an average hazard derived by excluding the acute period of the first month.

5.3.4 Health-related quality of life (HRQoL)

HRQoL is assessed in terms of utilities which are used to derive quality-adjusted life years (QALYs). Although HRQoL data based on SF-36 and IWQOL-Lite data were collected as part of the RIO trials, these were not used as the basis for estimating QALYs in the manufacturer's model. While published algorithms exist that would allow these measures to be converted to utilities, the manufacturer provides a number of reasons for preferring to use external evidence as the basis of the inputs into the model. These reasons include: (i) a lack of congruency between the health utility estimates from the SF-36 and IWQOL-Lite data from the RIO trials; (ii) the need to ensure consistency with other utility estimates (e.g. CVD events) applied in the model; and (iii) a preference for utilising data based on the EuroQol (EQ-5D) in accordance with the NICE reference case.

External utility estimates, based on the EQ-5D instrument, are thus used in the manufacturer's model. Each health state is assigned a utility estimate, which decrease as the cohort ages. Age-specific utilities for subjects without complications are based on EQ-5D scores obtained from a representative sample of the UK population taken from the 2003 Health Survey for England.[37] Utility decrements corresponding to the particular states of the model are then applied to the age-specific utility estimates. The health utilities applied in the Markov model are reported in Table 5.5.

Table 5.5: Health utility estimates

	Value	Source
Age specific utilities	Polynomial Equation[†]	Health Survey of England[37]
Per unit increase in BMI	-0.014	HODaR[35]
Stroke	-0.185	HODaR[35]
TIA	-0.088	HODaR[35]
MI	-0.072	HODaR[35]
Angina	-0.126	HODaR[35]
Type 2 diabetes	-0.041	HODaR[35]

[†] Utility = $1.20659185 - 0.01838271age - 0.00036882age^2 - 0.00000257age^3$

Utility decrements are applied to subjects in the DM and CVD states to account for the disutility associated with stroke, TIA, angina, MI and diabetes. These estimates are based on EQ-5D data from the HODaR dataset.[35] The HODaR dataset contains EQ-5D data from patients discharged (6-week post discharge) from the Cardiff and Vale NHS Trust in Wales.

An additional utility decrement is also applied per unit change in BMI. This assumption was also informed by the HODaR dataset based on an analysis of subjects with BMI ≥ 27 kg/m^2 adjusting for age, sex and diabetes status. The resulting estimate implies a 0.014 change in utility per unit change in BMI. No negative effects on health utility are assigned for adverse side effects associated with any treatment.

5.3.5 Resource utilisation and costs

Resource utilisation and costs in the economic evaluation are considered for: (i) treatment (including drug acquisition and monitoring costs), (ii) adverse effects, (iii) CVD complications, including acute and chronic events, and (iv) diabetes. The unit costs applied to these components are reported in Table 5.6. All costs are valued in 2005 GBP with the exception of drug costs which are based on current (2007) unit costs.

Treatment costs include the cost of drug acquisition and monitoring. Based on recommended dosages, the drug acquisition costs reported by the manufacturer are in accordance with those reported in the British National Formulary (BNF).[9] Compliance is based on utilisation of rimonabant in the RIO trials, and the number of days treated per year is assumed to be 262 for females without diabetes, 284 for males without diabetes, 288 for females with diabetes, and 293 for males with diabetes. Annual drug costs are therefore adjusted by these compliance levels. These same adjustments are applied to orlistat and sibutramine. Monitoring costs are added to the cost of the drug based on frequency of GP and nurse visits and are reported in Table 5.7.

Table 5.6: Unit costs applied in the Markov model

Element	Value (£)
Drug acquisition cost	
Rimonabant 20mg	1.57 per day
Orlistat 120 mg tid (or with each meal)	1.20 per day
Sibutramine 10-15 mg	1.41 per day
Complication costs	
Acute MI per event	1,366
Acute angina per event	1,183
Acute stroke per event	2,530
Acute TIA per event	952
Chronic MI per month	13.18
Chronic angina per month	7.37
Chronic stroke per month	21.20
Chronic TIA per month	20.14
Type 2 diabetes per month	31.70
Medical visits for treatment monitoring	
Nurse visit	15.75
Doctor visit	28.60
Adverse event costs for treated adverse events	
Anxiety per event	45.39
Mood alterations per event	48.00
Depressive disorders per event	42.96
Insomnia per event	22.60
Dizziness per event	24.10
Nausea per event	22.68
Diarrhoea per event	23.05
Vomiting per event	22.68
Contusion per event	21.48
Tendonitis per event	23.21

Table 5.7: Monitoring costs applied in the model

	Medical visit type	Frequency of use per year	Unit cost per visit (£)
Diet and Exercise	Doctor Visit	0	28.60
	Nurse Visit	4*	15.75
Rimonabant and Orlistat	Doctor Visit	4*	28.60
	Nurse Visit	0	15.75
Sibutramine	Doctor Visit	4*	28.60
	Nurse Visit	7**	15.75

* reported to be 3 in the original submission but corrected as part of the clarification response
** additional nurse visits based on blood pressure and pulse rate monitoring required for sibutramine

The costs of managing adverse events that may occur due to treatment use are obtained from routine NHS sources and national databases. The choice of treatment prescribed for each adverse event is based on information obtained in the NHS PRODIGY prescribing decision support database.[45] Where this information is unavailable, prescribing guidance is taken from the BNF. In calculating the corresponding prescription costs, the minimum effective dose is used to treat each adverse effect. The prescription costs themselves are calculated from the net ingredient cost of drugs specified in Part VIII – Basic Prices of Drugs of the NHS Electronic Drug Tariff.[46] Where multiple treatment options exist for a given condition, a weighted average is calculated by multiplying the cost of each option by a market share estimate.

Added to the prescription cost is a unit cost of one GP consultation at the surgery and a fixed cost paid to community pharmacists per prescription item dispensed. These unit costs are obtained from the PSSRU database.[47] The manufacturer assumes conservatively that adverse event costs for orlistat and sibutramine are equivalent to those for diet and exercise. These adverse event costs accrue for the duration of treatment.

The costs of managing CVD are differentiated by one-time acute care costs and long-term chronic management costs. The acute care costs reflect the resources consumed during the episode of the event. They include hospitalisation and post-acute care costs. The average inpatient length of stay is based on data from the Cardiff and Vale NHS trust. Healthcare Resource Groups (HRGs) are attributed to each admission and cross-referenced with NHS reference costs. Post-acute care costs are based on optimal care for each patient following current UK best practice guidelines. Patients who survive an acute CVD event are assumed to continue to accrue additional resources for follow-up and treatment. These are considered in the estimates of the costs of chronic management. Treatment choices for each chronic condition are made with reference to the NHS PRODIGY prescribing database. The lowest cost treatment option at the minimum effective dose is used to calculate prescription costs, which came from Part VIII - Basic Prices of Drugs of the NHS Electronic Drug Tariff. The costs of managing chronic MI referred to the recurring annual costs of preventing further MI in individuals who survived the first year after the index MI. The costs are based on NICE guidelines for post-MI prophylaxis. Similarly, the costs of managing chronic stroke referred to the annual costs of preventing further strokes in individuals who survived the first year after the index stroke. These costs are based on guidance from the Royal College of Physicians guidelines. Chronic costs of managing TIA are similar to that of stroke with post-acute care elements modelled as for mild stroke. Chronic costs of managing angina are based on guidelines indicated in the BNF 53 stating that patients should receive low dose aspirin indefinitely in addition to a suitable statin. The medical costs of managing diabetes, excluding the costs associated with CVD, are applied to the proportion of the cohort in the DM state. These costs are derived from the

UKPDS study and consisted of the sum of expected annual hospital inpatient and outpatient costs.

5.3.6 Discounting

The manufacturer applies an annual discount rate of 3.5% for future costs and QALYs.

5.3.7 Sensitivity analyses

The manufacturer's submission includes several one-way deterministic sensitivity analyses. A probabilistic sensitivity analysis (PSA) is also undertaken for the three base-case populations. For the PSA, a range of input parameters are varied by 30% in either direction with the exception of the treatment effectiveness variables, which are varied according to trial-based standard error estimates.

5.3.8 Model validation

The manufacturer's submission states that extensive testing of the model was conducted to ensure internal validity. They claim that the technical accuracy of the model was ascertained through extreme value testing of model inputs to identify unexpected model behaviour, comparing predicted model outcomes with simpler spreadsheet applications of the risk equations and by having an external programmer review the model and examine typing errors.

The validity of the model is also assessed by comparing model predictions using source data to results from other studies. The five year survival rates from the Saskatchewan dataset that were used to calculate post-CVD event rates and mortality are compared with five year survival rates from the SLIM database, which captures secondary care and mortality data for the Cardiff and Vale region of South Wales. The manufacturer claims that the results are comparable in all but one event category. Five year survival rates for stroke after a previous stroke occurrence are different between the two datasets, with survival probabilities significantly lower in SLIM. However, when stroke survival rates are compared with the CHKS database, which contains secondary care data for UK patients, the rates are more comparable

with the source data (Saskatchewan). A sensitivity analysis varying post-CVD event rates is conducted due to the discrepancy noted in stroke event rates. Additional comparisons are also reported to have been made using the CHKS database, which were shown to be more comparable to the Saskatchewan data. The predictive validity of CVD events from the model is also compared against published data and indicates a generally good level of predictive performance.

Finally, the manufacturer also present the results of the DES model which provides an additional validity check on the results based on the Markov model.

5.4 Critique of the manufacturer's economic evaluation

The ERG has considered the methods applied in the manufacturer's economic evaluation in the context of the critical appraisal questions listed in Table 5.8 which is drawn from common checklists for economic evaluation methods.[48]

Table 5.9 compares the manufacturer's submission to that of the NICE reference case.

A critical review of the methods used in the manufacturer's economic evaluation has been undertaken. The review has used the previous checklists as a basis for the analysis.

Table 5.8: Critical appraisal checklist

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	Yes	The manufacturer assessed the cost-effectiveness of rimonabant as an adjunct to diet and exercise for the treatment of obese patients (BMI ≥ 30 kg/m^2), or overweight patients (BMI > 27 kg/m^2) with associated risk factors such as type II diabetes or dyslipidaemia.
Is there a clear description of alternatives?	Yes	The relevant comparators to rimonabant considered were alternative pharmacological treatments (orlistat and sibutramine) and a non-pharmacological intervention of diet and exercise alone.
Has the correct patient group/ population of interest been clearly stated?	Yes	The population of interest is adult patients who are either obese, or who are overweight and either have diabetes or dyslipidaemia. This population is consistent with rimonabant's licensed indication in the UK. Three base-case populations and seven separate subgroup populations are defined.
Is the correct comparator used?	No	The duration of treatments assumed for orlistat and sibutramine are not in accordance with either their licence or previous NICE guidance. Patients are thus assumed to continue treatment with orlistat and sibutramine beyond 3 months regardless of whether they have achieved at least 5% reduction of the body weight as measured at the start of drug therapy.
Is the study type reasonable?	Yes	Cost-effectiveness analysis with quality-adjusted life years (QALYs) used as a measure of treatment benefit.
Is the perspective of the analysis clearly stated?	Yes	The economic evaluation states that costs were estimated from the perspective of the UK NHS and Personal Social Service (PSS), and health outcomes in terms of QALYs.
Is the perspective employed appropriate?	Yes	The manufacturer's submission adopts a UK NHS and PSS perspective for costs, which is consistent with the NICE reference case.
Is effectiveness of the intervention established?	?	The effectiveness of rimonabant is specified in terms of changes in BMI and other risk factor outcome measures from the RIO trials. Indirect comparison methods are used to obtain the relative effectiveness of orlistat and sibutramine since there are no head-to-head trials comparing rimonabant with these active comparators. There are concerns about the accuracy of the effectiveness estimates from the indirect comparison, given the simplicity of the approach used and the assumptions of exchangeability required. Also, due to an absence of response hurdles for drug discontinuation, it is difficult to assess the true incremental benefits of treatment with rimonabant. Furthermore, the model uses surrogate endpoints for extrapolation purposes and estimates outcomes using external published risk equations and other epidemiological sources.
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	Yes	A lifetime horizon has been used in the model with lifetime duration of treatment for rimonabant, orlistat, and diet and exercise. A one-year treatment duration is used for sibutramine in accordance with its licence.
Are the costs and consequences consistent with the perspective employed?	Yes	Costs are consistent with a NHS and PSS perspective. Consequences are measured in QALYs.
Is differential timing considered?	Yes	Future costs and health outcomes were discounted at an appropriate rate of 3.5% per annum.
Is incremental analysis performed?	?	Although an incremental analysis is performed, this is presented as a series of pairwise comparisons between the different interventions. No attempt is made to simultaneously compare the full range of treatments.
Is sensitivity analysis undertaken and presented clearly?	Yes	A number of one-way deterministic sensitivity analyses were undertaken and the results clearly presented (Section 6.3.3, p117; tables 49-51). A probabilistic sensitivity analysis was undertaken, but the parameters were mostly varied by an arbitrary range.

Table 5.9: NICE reference case checklist

Attribute	Reference Case	Included in submission	Comment on whether de-novo evaluation meets requirements of NICE reference case
Comparator(s)	Alternative therapies including those routinely used in NHS	No	The comparison with alternative pharmacological treatments (orlistat and sibutramine) and diet and exercise alone is appropriate as these reflect the treatments routinely used in the NHS. However, the duration of treatments assumed for orlistat and sibutramine are not in accordance with either their licence or previous NICE guidance and hence cannot be considered to represent how these strategies would be routinely used in the NHS.
Perspective -costs	NHS and PSS	Yes	NHS and PSS costs have been taken into account.
Perspective -benefits	All health effects on individuals	Yes	QALY benefits to treated individuals were considered.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	The economic model has a lifetime time horizon. Alternative time horizons are also explored.
Synthesis of evidence	Systematic review	?	The four RIO trials, which formed part of the RIO programme, were used to synthesise the evidence on the effectiveness of rimonabant and diet and exercise alone. A review was undertaken to obtain evidence on the effectiveness of orlistat and sibutramine with placebo, as an adjunct to diet and exercise. This facilitated an indirect comparison of the active comparators with rimonabant. The ERG identified a number of potential issues and limitations with this approach (see Section 4.3.4.1)
Outcome measure	QALYs	Yes	The model values all health in terms of QALYs using EQ-5D to measure health utilities.
Health states for QALY measurement	Described using a standardised and validated instrument	Yes	Utility values were based on EQ-5D scores from the 2003 Health Survey for England[37] and the HODaR dataset.[35] There is concern that whilst SF-36 and IWQoL-Lite data were available, collected as part of the clinical trial data in the RIO programme and converted to utilities using the SF-6D algorithm, these were not utilised in the original submission.
Benefit valuation	Time Trade Off or Standard Gamble	?	N.A.
Source of preference data	Sample of public	?	N.A.
Discount rate	Health benefits and costs	Yes	Benefits and costs have both been discounted at 3.5%.
Equity	No special weighting	Yes	No special weighting was undertaken.
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	Probabilistic sensitivity analysis was undertaken but the parameters are varied by an arbitrary range. Results are presented graphically using cost-effectiveness acceptability curves (CEACs).

5.4.1 Comparators

The manufacturer presents separate cost-effectiveness results for the following main comparisons:

- Lifetime rimonabant plus diet and exercise versus lifetime diet and exercise alone
- Lifetime rimonabant plus diet and exercise versus lifetime orlistat plus diet and exercise
- 1 year rimonabant plus diet and exercise versus 1 year sibutramine plus diet and exercise

Additional deterministic sensitivity analyses are presented for alternative treatment durations for rimonabant and orlistat (1, 5 and 10 years). Given that the comparison of rimonabant and sibutramine assumes a fixed one year duration for both, the alternative treatment durations (5 and 10 years) are not applied to this comparison.

The comparisons made by the manufacturer raise a number of important issues. Firstly, the manufacturer evaluates the incremental cost-effectiveness of rimonabant via a series of pairwise comparisons. However, this approach does not directly address the full decision problem, since this would require a simultaneous assessment of all relevant treatment options. Consequently, the incremental cost-effectiveness ratios (ICERs), as they are presented by the manufacturer, do not necessarily reflect the correct estimate of the ICER for rimonabant. The correct approach requires the mean lifetime costs and QALYs of all the relevant strategies to be compared simultaneously and their cost-effectiveness assessed, estimating ICERs as appropriate (i.e. establishing whether particular treatments are ruled out on the grounds of dominance or extended dominance), using standard decision rules.[49] This also has important implications for the probabilistic sensitivity analysis and the representation of decision uncertainty using cost-effectiveness acceptability curves. Since the decision itself concerns the relative cost-effectiveness of rimonabant compared to several alternative treatments, the representation of decision uncertainty using a series of pairwise comparisons is potentially misleading. These problems are exacerbated by the different durations of treatment modelled using rimonabant (lifetime in the comparison with orlistat and diet and exercise alone and 1 year in the comparison with sibutramine). Consequently, the separate analyses presented by the manufacturer are not directly comparable since they involve different assumptions in relation to the duration of treatment with rimonabant. This problem compounds the difficulties of interpreting the ICERs of rimonabant based on the pairwise comparisons presented by the manufacturer.

A second major issue relates to the choice of comparators included by the manufacturer (orlistat and sibutramine in conjunction with diet and exercise and diet and exercise alone). While these comparators clearly reflect the relevant alternatives to rimonabant, the ERG has concerns about how these comparators have been interpreted by the manufacturer in their submission. In particular, the ERG notes that the manufacturer's assumption regarding the use of sibutramine or orlistat applied in the model are neither in accordance with their respective licences or previous NICE guidance on the management of obesity. Existing NICE guidance for orlistat and sibutramine clearly states that withdrawal of anti-obesity drug treatment should be considered in people who do not lose enough weight and specifically that:

- 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. (See also recommendation for advice on targets for people with type 2 diabetes.)
- 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.

Regarding longer term treatment, NICE guidance states for orlistat that 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, while for sibutramine, treatment is not currently recommended beyond the licensed duration of 12 months.

Consequently the ERG does not consider that the approach to modelling sibutramine or orlisat reflects how these drugs are currently used in the NHS, since both drugs currently require a response 'hurdle' (5% weight loss) to be met in order for the drug to be continued beyond 3 months. Although the ERG is aware that rimonabant's product licence does not require a similar response 'hurdle' at 3 months, this should not alter the manufacturer's approach to

modelling the relevant comparators. Previous models have demonstrated large differences in the ICER of orlistat compared to diet and exercise alone based on comparisons with and without the response 'hurdle' implemented.[50, 51] These models have concluded that the continuation of orlistat in non-responders at 3 months does not appear to be cost-effective. Therefore, by comparing a lifetime of drug treatment on rimonabant to a lifetime of drug treatment on orlistat (which has no response hurdles implemented), the manufacturer may be overstating the cost-effectiveness advantage of rimonabant. The same conclusions are also likely to relate to the comparison with sibutramine.

The ERG believes that the manufacturer should have compared rimonabant with strategies involving orlistat and sibutramine with a response 'hurdle' implemented, whereby treatment is continued beyond 3 months only in those patients who responded. This would ensure consistency with current NICE guidance and their respective product licences. Discussions with the ERG's clinical advisor strongly supported the view that patients who have not responded to a reasonable weight loss by 3 months are unlikely to continue to receive an anti-obesity drug indefinitely.

In addition to the issues noted in relation to the comparator drugs considered in the manufacturer submission, the ERG is also concerned about the manufacturer's approach to modelling rimonabant itself. As it currently stands in the manufacturer's submission, their economic evaluation is based on a continuation of rimonabant treatment over the patient's lifetime (or 1 year in the comparison with sibutramine) regardless of the patient's response status. While the ERG acknowledges the absence of the 3 month response 'hurdle' in rimonabant's licence, the *cost-effectiveness* of alternative durations of treatments for rimonabant with and without alternative response hurdles has not been adequately demonstrated. Consequently, the ERG believes it would have been appropriate for the manufacturer to have considered a range of potential rimonabant strategies employing alternative assumptions about continuation (e.g. strategies employing a response 'hurdle' at 3, 6, 9 and 12 months). This approach would then clearly demonstrate the incremental cost-

effectiveness of either extending the response 'hurdle' beyond 3 months for rimonabant or removing the response 'hurdle' altogether.

In conclusion, the ERG considers that the existing manufacturer submission does not correctly model the full range of relevant strategies for the comparator drugs considered (and also potentially for rimonabant). As such, the relevance of the subsequent ICER's presented by the manufacturer needs to be considered carefully.

5.4.2 Subgroups

As previously stated in Section 5.3, the manufacturer presents the cost-effectiveness results for three base case populations. Additional sensitivity analyses are also presented in relation to specific subsets of the population. The ERG notes that the selection of the base case populations was principally driven by the relevant inclusion/exclusion criteria applied in the RIO trials as opposed to basing these on the most clinically and/or policy relevant populations for the economic model. For example, two of the main base case populations presented in the submission relate to: (i) overweight / obese patients with treated type 2 diabetes (uncontrolled with metformin or sulfonylurea) and (ii) overweight/obese patients with untreated dyslipidaemia. While these populations closely match the design RIO-Diabetes and RIO-Lipids trials respectively, the ERG recognises that these populations are not necessarily the most policy relevant populations for the cost-effectiveness analysis. This has potential implications for the cost-effectiveness results which follow, particularly since patients who failed to achieve adequate glycaemic control with existing anti-diabetic medication or with untreated dyslipidaemia would potentially receive alternative treatments (e.g. alternative anti-diabetic medication, statins etc) in routine clinical practice. As such, it is possible that the results are likely to overstate the potential cost-effectiveness of the anti-obesity drugs examined in these populations. The ERG recognises that these issues are partially addressed as part of the manufacturer's sensitivity analysis, in which additional analyses are presented for overweight/obese patients with treated dyslipidaemia. However, concerns remain as to whether patients with inadequately controlled diabetes are likely

to be switched to an alternative anti-diabetic medication and the potential impact that this might have on the cost-effectiveness results.

Although a number of separate subgroups were considered by the manufacturer, the ERG identified two subgroups which had not been considered: (i) obese patients with treated dyslipidaemia and no diabetes and (ii) obese patients without either dyslipidaemia or diabetes. In their response to the ERG points for clarification, the manufacturer stated that a formal comparison of these populations was not possible within the time available. However, the manufacturer commented on the consistency in the ICERs between overweight patients with treated and untreated dyslipidaemia, suggesting that the ICERs for these missing subgroups were not likely to differ markedly from the estimates presented.

5.4.3 Treatment effectiveness

The validity of the manufacturer's approach to treatment effectiveness is dependent upon a number of separate (and related) assumptions used by the manufacturer. These include:

1. In the absence of direct head-to-head RCT data, the relative effectiveness of the different comparators can be compared using indirect approaches.
2. Treatment effects at 1 year are maintained for the duration of treatment (lifetime in the base case).
3. Treatment effects accrue linearly during the first 9 months of treatment at which point they reach their maximum. Once treatment is stopped, the treatment effect is lost over the course of a year (assumed to decrease linearly over 12 months).
4. Changes in the risk factors for CVD and diabetes result in a reduction in the associated risk of these complications in the longer term.
5. HRQoL is influenced by weight change (modelled via BMI) independently of any impact on the risk of CVD and diabetes.

The ERG have previously discussed (Section 4.1.7.6) a number of issues and concerns related to the indirect comparisons presented by the manufacturer and the assumptions related to the exchangeability of the different studies. In addition to these more general points, the ERG also identified several specific issues which relate to how this data is subsequently employed in the economic model. Firstly, there were a number of subgroups for which relevant data did not appear to be available for orlistat and/or sibutramine. In the absence of this data, these comparators were excluded entirely from the manufacturer's economic analysis. Consequently, the full range of treatment alternatives was not considered in each of the separate subgroups. Secondly, there is a lack of transparency in some of the inputs used in the economic analysis. For example, within particular subgroups, estimates from the meta-analysis were not available for every risk factor considered in the model (e.g. HbA_{1c}). Examination of the electronic model revealed that, in these cases, estimates had been entered in the economic model but without any explanation as to either their source or details of how they were derived.

In addition, the ERG also identified a potentially important inconsistency between the results of the meta-analysis for orlistat in relation to change in BMI and the data employed in the model (presented in Table 21, page 67 of the manufacturer submission and Appendix 6, page 105 of the manufacturer appendices). While the results of the change in BMI estimated from the meta-analysis is reported in Table 21 (-2.1 95% CI -4.25 to 0.05), a separate estimate is subsequently used in the economic model. A footnote on page 105, Appendix 6 of the manufacturer's submission reports that "Orlistat BMI data were calculated from the rimonabant BMI data assuming the ratio derived from the WMD for weight change observed between the RIO and orlistat trials – this was done because limited BMI data were available in comparison to weight data". The ERG notes that the subsequent estimate assumed for orlistat using this approach is less favourable than the results from the meta-analysis itself for the subgroup equivalent to RIO-Diabetes. Given the importance of BMI in the context of the economic model, the ERG felt that the company could have been more explicit regarding the assumptions employed and their decision to use alternative values. In

addition, the ERG considered that additional sensitivity analysis should have been used to explore this issue. These points reflect a general concern from the ERG that there is a lack of transparency surrounding the results of the indirect comparisons and how they have subsequently been applied in the economic model.

The assumption regarding the maintenance of treatment effects in the long-term are likely to be a key driver of cost-effectiveness. The manufacturer assumes that the benefits in the longer-term will be maintained at the same level as achieved at 1-year. The ERG considers that this is an optimistic assumption and that, while the results at 2-years indicate that patients continued to show statistically significant weight loss compared to baseline, the mean differences were generally less favourable than the 1 year results. Consequently, the ERG considers that this assumption is an important source of uncertainty in the manufacturer's submission and that additional sensitivity analysis should have been undertaken to examine the robustness of the base-case results to this assumption.

The assumption that treatment effects accrue linearly during the first 9 months of treatment to a maximum is based on findings from the RIO trials for rimonabant. In the absence of similar data for orlistat and sibutramine the manufacturer applies this assumption to all treatments. Since it is unclear whether a similar treatment lag applies to these other treatments, the manufacturer presents the results of a sensitivity analysis involving shorter periods (6 months) of time over which the maximum treatment effect accrues. However, given that the current licences for orlistat and sibutramine require the drugs to be discontinued at 3 months if a 5% weight loss has not been achieved, the ERG considers that shorter durations (e.g. 3 months) could have been presented for the comparators as a conservative sensitivity analysis.

The manufacturer also assumes that once treatment is stopped, the treatment effect is lost over the course of a year. Although this assumption will not affect the comparison between rimonabant, orlistat and diet and exercise

(since the manufacturer assumes that patients remain on treatment for a lifetime), this assumption does have a potential impact on the comparison between rimonabant and sibutramine which are both compared on the basis of 1 year treatment duration. The ERG notes that the assumption is based on findings from the RIO trials and the generalisability of this estimate to sibutramine is not clear. However, discussion with the ERG's clinical advisor indicates that there are unlikely to be significant differences between treatments in the rate of weight gain after treatment is discontinued.

The issues related to the risk equations and HRQoL are addressed separately below (Sections 5.4.4 and 5.4.5).

5.4.4 Transition probabilities

A central component of the manufacturer's submission is the assumption that the effect of treatment on weight loss and other intermediate outcomes result in a reduction in the associated risk of complications in the longer term. This is a particularly important assumption given the lifetime duration of treatment proposed for rimonabant and orlistat. We have previously identified the lack of direct evidence on the impact of rimonabant on the risk of CVD and/or diabetes. In the absence of direct evidence, the manufacturer employs a series of published risk equations to link the effect of rimonabant (and other treatments) on individual risk factors to the risk of diabetes and CVD. No attempt was made by the manufacturer to evaluate the potential impact of anti-obesity treatments on other complications potentially associated with obesity, such as muscolskeletal disorders, respiratory diseases and cancers. These were not included since the manufacturer did not consider them to be directly related to rimonabant's licensed indication. Furthermore, the company state that their exclusion means that the resulting cost-effectiveness estimates are likely to represent conservative estimates.

In general the ERG accepted that, in the absence of direct evidence in relation to the effect of rimonabant on 'hard' clinical endpoints, the approach used by the manufacturer was appropriate for the purpose of the cost-effectiveness analysis. However, the ERG felt that there was a lack of clarity regarding the

rationale for selecting particular risk equations and little discussion regarding how these had been identified. Furthermore there was insufficient detail presented to assess their generalisability to the population of interest.

While the ERG recognises that the risk equations chosen (in particular the FHS and UKPDS) are well established in their respective areas, the ERG feels that there is scant contextual information provided to establish whether there are viable alternative risk equations, which may estimate different relationships for some of the key risk factors considered. Additional clarification was, therefore, sought by the ERG in relation to the justification used by the manufacturer to select the particular risk equations. However, only limited additional information was reported by the manufacturer, simply stating that risk equations were "selected based on whether they captured the effects of relevant risk factors on the risk of developing cardiovascular disease and diabetes, and their appropriateness for the populations being assessed" (p58 Manufacturer's response to clarification questions, September 2007). Given the importance of the risk equations in the context of the economic model, the ERG considers that additional information and a more detailed critique of the equations used would have helped to confirm the relevance of the equations used.

It is worth highlighting that several of the risk equations are derived from observational datasets dating back to as early as the 1970s and are based on non-UK populations. Consequently, their applicability as a source of contemporary event rates relevant to the UK needs further consideration by the manufacturer. For example, risk scores based on the FHS reflect the higher risks of cardiovascular disease in the 1970s and 1980s (due to the limited use of primary preventative treatments such as statins) and have been shown to over-predict current risks.[52] The estimates of CHD/CVD risks from Framingham are thus more likely to represent the risks of an untreated population. However, clearly the population of interest considered by the manufacturer will include both treated and untreated subjects. A more contemporary cardiovascular risk equation developed for the UK, the QRISK score, has recently been validated against the FHS.[52] The equations based

on the FHS were reported to over-predict events by 35%, compared to 0.4% by the QRISK. Furthermore, the hazard ratio estimated for BMI in the QRISK risk score suggests a smaller effect than that assumed by the manufacturer based on the adjustment to FHS reported by Mora et al.[33] In QRISK, a unit change in BMI was reported to increase the risk of an event by 1.5% in females and 2.2% in males. This contrasts with the 3.77% increase applied per unit change in BMI by the manufacturer to the predicted risk from FHS. Consequently, the estimates using particular risk equations in the manufacturer's model may over-estimate the risk of events and, more importantly, without adjustment for current treatment patterns in relation to primary prevention strategies, the manufacturer may also over-estimate the impact of changes in particular risk factors to the overall risk of events.

In conclusion, the ERG considers that there are a number of important uncertainties surrounding the risk equations employed in the manufacturer's model and that a more transparent and critical approach would have provided greater reassurance in relation to the underlying estimates applied in the model. The ERG does, however, acknowledge that some of these uncertainties have been considered by the manufacturer. In addition to the validation exercises, the manufacturer also varied the CVD risk scores (+/- 50%) and applied several adjustments to the FHS scores as part of their sensitivity analysis. While none of these changes appeared to significantly alter the ICER estimates, it should also be noted that these alternative assumptions were explored using 1-way deterministic analyses (and in a limited range of subgroups), such that assumptions were varied one at time. Data from QRISK suggests that 2-way sensitivity analysis could provide more conservative estimates, such that the impact on the ICER of changes in the absolute risk of CVD events in conjunction with an attenuated impact of particular risk factors could be considered.

5.4.5 Health-related quality of life (HRQoL)

There are three major issues arising from the manufacturer's approach to modelling HRQoL: (i) the decision to employ external utility estimates as opposed to utilising the HRQoL data reported in the RIO trials; (ii) the

relationship assumed between BMI changes and utility (assumed to result in a 0.014 improvement in utility per point reduction in BMI); and (iii) the disutility assigned to events themselves (e.g. diabetes, CVD events). Each of the issues is discussed in detail below.

As previously outlined, the manufacturer's model employs external utility estimates to populate the model as opposed to utilising the HRQoL data in the RIO trials which incorporated both generic (SF-36) and obesity-specific (IWQoL-Lite) measures of QoL. The manufacturers justify the use of external estimates on several grounds (see Section 5.3.4), including the finding that the SF-36 and IWQoL-Lite data from the RIO trials did not appear to provide congruent evidence of the impact of rimonabant on health utility. While the ERG acknowledges these points, the ERG also considers that the lack of congruence between the findings of the alternative HRQoL instruments reported in the RIO trials has not been adequately explained or investigated by the manufacturer. Hence, the ERG feels that the existing HRQoL data from the RIO trials has not been sufficiently considered by the manufacturer or the potential implications that this may have for the cost-effectiveness results presented in their submission.

As previously described, HRQoL was assessed in the RIO trials using the generic SF-36 and an obesity specific instrument, IWQoL-Lite. Scores from both instruments were available at baseline and every three months up to one year for participants in the RIO programme. These scores were transformed into utilities using different forms of the SF-6D algorithm for both instruments.[17, 18] The results are presented in Tables 5.10 and 5.11.

In highlighting the lack of congruence between the measures, the manufacturer noted a general improvement in the IWQoL-Lite utility values from baseline to 1 year in both the rimonabant and placebo groups, but observed a general decline in the values derived from the SF-36 in both treatment arms. Based on the results from the pooled RIO studies, rimonabant showed a mean [redacted] in utility of [redacted] compared to placebo based on the IWQOL-Lite data and a mean [redacted] in utility of [redacted] based on

the SF-36 data. The manufacturer concluded that the SF-36 possibly fails to detect meaningful or consistent differences across the health domains in this population, and that the discrepancy may be due to factors other than treatment.

Table 5.10: Change from baseline at 1 year in IWQOL-lite scores. Difference in change between placebo & rimonabant – ITT population, pooled RIO studies (4 studies).

Domain	Treatment	n	Change from baseline (95% CI)	Effect Size	Unadjusted difference	LSMEANS (adjusted difference) (95% CI)
Physical function	Placebo	1584	4.99 ( )	0.26	3.85	
	Rimonabant	2470	8.84 ( )	0.45		
Self-esteem	Placebo	1584	8.05 ( )	0.33	2.72	
	Rimonabant	2461	10.76 ( )	0.43		
Sexual life	Placebo	1533	3.45 ( )	0.15	1.49	
	Rimonabant	2397	4.93 ( )	0.22		
Public distress	Placebo	1587	2.17 ( )	0.13	1.83	
	Rimonabant	2479	4.00 ( )	0.22		
Work	Placebo	1579	3.19 ( )	0.18	0.77	
	Rimonabant	2469	3.96 ( )	0.23		
IWQOL-Lite total	Placebo	1576	4.77 ( )	0.28	2.58	
	Rimonabant	2461	7.35 ( )	0.44		
Utility	Placebo	1496	0.019 ( )	0.25	0.012	
	Rimonabant	2347	0.032 ( )	0.375		

**p-value<=0.01, * p-value<=0.05 rimonabant compared to placebo. Statistical comparisons individual scores changes at 1 year were analysed using an Analysis of Variance with covariates (ANCOVA). The endpoint for each domain was the change from baseline value at 1 year; the fixed effects were the treatment group and the value of the score at baseline. For the pooled study, a study fixed effect was added as covariate.

Table 5.11: Changes from baseline at 1 year in SF-36 scores; difference in change between placebo and rimonabant ITT population, pooled RIO studies

Domain	Treatment	n	Change from Baseline (95% CI)	Effect Size	Unadjusted difference	LSMEANS (adjusted difference) (95% CI)
Physical functioning	Placebo	1414	2.78 ( )	0.13	2.76	
	Rimonabant	2229	5.54 ( )	0.26		
Role physical	Placebo	1418	-2.9 ( )	-0.10	0.03	
	Rimonabant	2212	-2.86 ( )	-0.10		
Bodily pain	Placebo	1423	-3.27 ( )	-0.15	1.51	
	Rimonabant	2232	-1.77 ( )	-0.08		
General health	Placebo	1398	-1.24 ( )	-0.07	1.32	
	Rimonabant	2205	0.09 ( )	0.01		
Vitality	Placebo	1416	-1.88 ( )	-0.10	0.55	
	Rimonabant	2233	-1.33 ( )	-0.07		
Social functioning	Placebo	1427	-3.78 ( )	-0.20	-0.39	
	Rimonabant	2242	-4.17 ( )	-0.23		
Role emotional	Placebo	1411	-5.58 ( )	-0.23	-2.16	
	Rimonabant	2209	-7.73 ( )	-0.31		
Mental health	Placebo	1417	-3.06 ( )	-0.21	-1.92	
	Rimonabant	2233	-4.98 ( )	-0.33		
Utility	Placebo	1269	-0.012 ( )	-0.09	-0.003	
	Rimonabant	2014	-0.014 ( )	-0.10		

**p-value<=0.01, * p-value<=0.05 rimonabant compared to placebo. Statistical comparisons individual scores changes at 1 year were analysed using an Analysis of Variance with covariates (ANCOVA). The endpoint for each domain was the change from baseline value at 1 year; the fixed effects were the treatment group and the value of the score at baseline. For the pooled study, a study fixed effect was added as covariate.

The ERG recognises the manufacturer's concern over the disparity between the instruments, but it would recommend further exploration of these differences in order to understand more fully the potential implications of these studies. The ERG notes that the SF-36 has been widely used in obesity studies and hence is concerned that these apparently contradictory findings are not explored in more detail. In relation to the SF-36 data, the ERG notes the significant improvement in particular dimensions (physical functioning, bodily pain, general health) reported for rimonabant compared to placebo but also the significant reduction in the role emotional and mental health dimensions of the SF-36. It is possible, therefore, that the positive improvements reported in several of the dimensions are offset by the negative impact on others when the scores for particular items across the different dimensions are combined using the SF-6D scoring algorithm. As such it is possible that the findings may not be inconsistent, particularly given the broader focus of the SF-36 compared to IWQOL-Lite. The ERG therefore considers that the potential impact of rimonabant on the role emotional and mental health dimensions needs further consideration by the manufacturer before these findings can be dismissed.

Focussing on the external evidence used by the manufacturer, the most important consideration is the relationship assumed between BMI and utility. This relationship is implemented in the model using two separate assumptions: (i) BMI change has a direct and independent impact on utility (i.e. over and above the effect that BMI has on the events predicted in the model); (ii) BMI also indirectly effects utility through the risk of developing diabetes and CVD events (i.e. BMI influences events which influences utility). Both assumptions are estimated empirically using the data from HODaR.

The independent relationship assumed for BMI was derived from a multivariate analysis of a subset of HODaR subjects with a BMI ≥27 kg/m^2 adjusting for age, sex and diabetes status. The resulting change in utility of 0.014 per unit change in BMI is reported by the manufacturer to be comparable to other published estimates. However, while reference is made

to the value assumed in the NICE guidance related to orlistat (0.017), no further data are provided by which to validate this figure.

Utility decrements estimated for subjects with complications (diabetes, CVD events) were based on a separate multivariate analysis of a wider set of patients in HODaR, comprising patients with and without a hospital admission with a primary diagnosis of the relevant disease state and recording diabetes status. Again, no comparisons with other published studies estimating the decrement of these particular events were made by the manufacturer and hence it is difficult to assess the validity of the subsequent estimates.

The ERG identified a number of potential concerns relating to the approach used by the manufacturer:

1) The manufacturer does not attempt to assess the validity of the resulting change in utility per unit change in BMI (or the impact of complications) in relation to estimates from other published studies.
2) Separate regressions appear to have been used to estimate the two main assumptions. However, a single regression adjusting for BMI and events simultaneously may provide a better model fit and may also attenuate the BMI coefficient identified using separate regressions.[53]
3) The utility values from HODaR are based on a cross-sectional survey that associates *levels* of BMI with utility, and hence does not directly assess the effect that *changes* in BMI may have on utility.

The ERG concludes that the manufacturer's approach to populating utility values in the model is subject to a number of uncertainties. These uncertainties are increased since no attempt is made to validate these results against other published estimates reporting the relationship between BMI and utility.

5.4.6 Resource utilisation and costs

In general, the ERG considers that the manufacturer's approach to resource utilisation and costing is appropriate. Some of the assumptions employed in relation to the monitoring costs were not considered to be sufficiently

transparent (particularly the additional frequency of nurse visits assumed for sibutramine), although subsequent clarification received from the manufacturer provided additional justification. The approach to estimating the acquisition costs was identified as a potentially important issue by the ERG. Rather than modelling compliance directly, the manufacturer adjusted the annual costs of each of the drug treatments based on the number of days of treatment per year reported across the RIO trials. This approach assumes that compliance rates in the trials of orlistat and sibutramine were similar to those reported in the RIO trials. In addition, the approach assumes that there was no wastage (i.e. patients prescribed medication but then did not subsequently take it, which would mean that the costs had still been incurred). However, the ERG notes that the manufacturer undertook a sensitivity analysis assuming that patients received 365 days of treatment which, in part at least, addresses these concerns. The ERG also recognises that the approach used to costing adverse events represents a conservative assumption by the manufacturer. The ERG was unsure as to the rationale of using resource use estimates for the acute health states using data from HODaR as opposed to using the HRG estimates directly however, the ERG did not consider this to be a significant issue.

5.4.7 Sensitivity analysis

The manufacturer presents a detailed set of deterministic analyses. Several of these scenarios consider a number of the issues identified by the ERG in their critique of the submission. However, the ERG felt that there were some potentially important omissions in relation to the following aspects:

- The assumptions used to estimate risk factor changes for orlistat and sibutramine where data were missing or considered to be insufficient (See Section 5.4.3).
- The long term assumption related to the maintenance of treatment effect after 1-year.
- Scenarios which would help to clarify the relative importance to the ICER estimates of the direct BMI/HRQoL assumption.

- Scenarios relating to the impact that changes in the risk factors have on the rate of complications. That is, a scenario which considered the ICER of rimonabant with and without the assumptions relating changes in risk factors to the events.

The ERG notes that 1-way sensitivity analyses were used to assess the impact of alternative assumptions. While the majority of these analyses only had a minor impact on the ICER estimates, it is unclear what impact these may have in combination. Consequently, the robustness of the cost-effectiveness results would have been reinforced by using multi-way sensitivity analyses and/or scenarios with best case/worst case assumptions.

The manufacturer also presented the results of a probabilistic sensitivity analysis (PSA). However, this is subject to a number of potential limitations. Firstly, a number of parameters were simply varied by an arbitrary range. Secondly, uncertainty in the risk equations themselves was not considered in the PSA, presumably due to the lack of published estimates reporting the standard errors of the coefficients and the variance-covariance matrix which would be required to model the correlation in a PSA between the individual risk factors. Furthermore, a number of the deterministic sensitivity analyses are based on alternative assumptions which are not adequately captured by the distributions attached to the parameters in the PSA.

5.5 Results included in manufacturer's submission

Tables 5.12 and 5.13 summarise the incremental cost-effectiveness of rimonabant versus each of the alternative comparators in the 3 base case populations and the additional subgroups considered. Across the base case populations, the ICER of rimonabant varied between £10,534 to £13,236 per QALY (versus diet and exercise), £8,977 to £12,138 per QALY (versus orlisat) and £1,463 to £3,908 per QALY (versus sibutramine). In the additional subgroups considered there was a wider variation in the ICER estimates. However, none of the individual pairwise ICERs for rimonabant exceeded £20,000 per QALY in any of the subgroups

.

Table 5.12: Summary of cost per QALY results in the base case patient populations

	Versus Diet and Exercise	Versus Orlistat	Versus Sibutramine
Overweight with treated diabetes (diabetic group)	£13,236	£9,924	£3,908
Overweight patients with untreated dyslipidaemia, no diabetes (dyslipdaemic group)	£10,543	£12,138	£1,463
All obese patients	£10,959	£8,977	N/A

Table 5.13: Summary of cost per QALY results in the additional subgroups

All obese and all overweight with diabetes or dyslipidaemia	£11,003	£17,503	£5,963
Overweight with treated dyslipidaemia	£14,840	£15,163	£1,605
Overweight patients with treated diabetes and HbA_{1c}<7	£15,950	N/A	N/A
Overweight patients with treated diabetes and HbA_{1c} ≥7	£12,971	N/A	N/A
Overweight patients with treated diabetes and HbA_{1c} ≥=8	£14,278	N/A	N/A
All obese patients with treated diabetes	£13,793	£15,317	N/A
All obese patients with untreated dyslipidaemia	£10,607	£6,783	N/A

The results of 23 deterministic, one-way sensitivity analyses were presented by the manufacturer for the 3 base-case populations (pages 118-120 of their submission). The ICER estimates across the majority of these analyses were broadly consistent with the base-case results. However, in several of these, the ICER of rimonabant increased to over £20,000 per QALY. These included the following scenarios:

- Treatment benefit lag reduced to 6 months for comparator (£38,896 vs sibutramine in the diabetic group).
- No BMI effect on utility (£22,969 vs diet and exercise and £27,873 vs sibutramine in the diabetic group; £21,637 vs diet and exercise and £32,375 vs orlistat in the dyslipdaemic group; £20,081 vs diet and exercise in all obese patients).

The results of the probabilistic sensitivity analyses was presented using a series of scatterplots and cost-effectiveness acceptability curves representing the separate pairwise comparisons against diet and exercise, orlistat and sibutramine (pages 122-126 of the manufacturer's submission). The results suggested that rimonabant had a very high probability of being cost-effective at a threshold of £30,000 per QALY (over 90% in the 3 base case populations).

5.6 Comment on validity of results presented with reference to methodology used

The manufacturer's results indicate that the ICER of rimonabant is likely to be less than £20,000 per QALY based on a wide-range of alternative assumptions. These conclusions were most sensitive to the assumption related to the treatment benefit lag and the assumption that BMI has an independent impact on HRQoL. The validity of these findings is subject to a number of potential uncertainties outlined by the ERG in this section. These are summarised below.

5.7 Summary of uncertainties and issues

In general, the ERG considered the manufacturer's economic submission to be of reasonable quality. The economic model structure was considered appropriate for the decision problem, and the manufacturer appears to have validated a number of particular elements (including presenting results using separate modelling approaches). Furthermore, the manufacturer has considered a wide range of alternative assumptions using a series of sensitivity analysis and has also considered variation in the ICER estimates in different patient subgroups. However, the ERG considers that the original submission has a number of important uncertainties and issues which may compromise the validity of the model results, including:

1. No simultaneous comparison of all relevant treatments.
2. The use of alternative assumptions regarding the duration of rimonabant treatment employed in the comparison against diet and exercise and orlisat to that used in the comparison with sibutramine, making a direct comparison between the results problematic.
3. The absence of response hurdles for orlistat and sibutramine.
4. A lack of transparency in the indirect comparisons used in the economic model.
5. The maintenance of treatment effects assumed in the longer term.
6. Uncertainty surrounding the divergence in HRQoL estimates based on the SF-36 and IWQOL-Lite data reported in the RIO trials.

7. The independent effect of BMI and health utility assumed in the model.
8. Uncertainty surrounding the selection of risk equations and their relevance to contemporary settings.

Given the importance of a number of these issues, several additional analyses were requested by the ERG to be undertaken by the manufacturer. These are considered in more detail in the next section, alongside a critique of these analyses and additional analyses undertaken by the ERG to address any remaining uncertainties.

6 Additional analyses undertaken by the manufacturer and the ERG

6.1 Overview

The ERG requested several additional analyses from the manufacturer to address a number of the key issues and uncertainties identified during the structured critique of their submission. This section provides details of the manufacturer's response together with a critical appraisal of the submitted evidence. Where uncertainties remained, additional analyses have been undertaken by the ERG to provide further insight into the potential impact on the cost-effectiveness estimates for these aspects.

This section focuses on the key issues identified by the ERG in Section 5. These have been separated into 3 main elements:

1. The lack of a simultaneous comparison between rimonabant and the full range of comparators.
2. The absence of response hurdles in the economic model.
3. Uncertainty related to the HRQoL estimates.

An additional analysis was also undertaken by the ERG to clarify the relative importance of the independent effect of BMI on utilities compared to the impact of the other risk factors on the CVD and diabetes event rates in the ICER estimates.

6.2 Simultaneous comparison of all relevant treatments

As outlined in Section 5.4.1, the manufacturer's submission evaluates the incremental cost-effectiveness of rimonabant via a series of pairwise comparisons. In doing so, they do not directly address the full decision problem, which requires a simultaneous assessment of all relevant treatment options. The ERG therefore requested a simultaneous comparison of rimonabant (lifetime treatment duration), orlistat (lifetime treatment duration), sibutramine (1-year treatment duration) and diet and exercise, as opposed to the separate pairwise comparisons presented in the original submission.

Manufacturer's response

As part of the manufacturer's response to the points for clarification, they provided a simultaneous comparison of rimonabant, orlistat, diet and exercise (all lifetime treatment duration) and sibutramine (1-year treatment duration) for 2 base-case populations and 2 sensitivity analysis populations. These populations represent the scenarios in which data were available to compare the full range of relevant strategies. The results of these analyses are summarised in Table 6.1. Based on these results, the manufacturer concluded that rimonabant is cost-effective when all treatments are compared simultaneously. It should be noted that PSA was not possible for these comparisons due to the way the model had been structured, requiring strategies to be run separately in the model.

Table 6.1: Simultaneous comparison of treatment strategies by the manufacturer

Base case 1: Overweight with treated diabetes				
Treatment	**Costs**	**QALYS**	**ICER**	
Rimonabant - lifetime	£13,287,230	9894.3	£9,924	versus orlistat
Orlistat - lifetime	£11,012,437	9665.1	£16,128	vs diet and exercise
Diet - lifetime	£6,779,115	9402.6	£37,051	versus sibutramine
Sibutramine 1 year	£5,861,412	9377.8	Least effective	
Base case 2: Overweight with untreated dyslipidaemia				
Treatment	**Costs**	**QALYS**	**ICER**	
Rimonabant - lifetime	£12,341,535	14382.6	£12,138	versus orlistat
Orlistat - lifetime	£9,426,205	14142.4	£9,880	vs diet and exercise
Diet - lifetime	£3,713,588	13564.2	£4,929	versus sibutramine
Sibutramine 1 year	£2,161,538	13249.3	Least effective	
Sensitivity analysis 1: Overweight with either diabetes or untreated dyslpidaemia or obese				
Treatment	**Costs**	**QALYS**	**ICER**	
Rimonabant - lifetime	£12,445,800	13549.4	£17,503	versus orlistat
Orlistat - lifetime	£9,679,306	13391.4	£9,243	vs diet and exercise
Diet - lifetime	£4,283,260	12807.6	£7,364	versus sibutramine
Sibutramine 1 year	£2,791,017	12605.0	Least effective	
Sensitivity analysis 2: Overweight with treated dyslipidaemia				
Treatment	**Costs**	**QALYS**	**ICER**	
Rimonabant - lifetime	£9,654,395	10299.5	£15,163	versus orlistat
Orlistat - lifetime	£7,730,777	10172.6	£14,697	vs diet and exercise
Diet - lifetime	£3,504,875	9885.1	£12,472	versus sibutramine
Sibutramine 1 year	£2,528,209	9806.8	Least effective	

Critique of manufacturer's response

The simultaneous comparison provided by the manufacturer in Table 6.1 demonstrates potentially counter-intuitive results. In particular, the finding that sibutramine is the least effective strategy (even less effective than diet and exercise) lacks face validity. Closer examination by the ERG of the electronic model submitted by the manufacturer revealed that different approaches were used to model the comparison of rimonbant, orlistat and diet and exercise to that employed in the comparison of rimonabant and sibutramine. In the first of these comparisons, the manufacturer compares each of the strategies by applying the mean change in risk scores for each of the strategies to the initial 'pre-treatment' baseline risk profiles. Since all treatments are assumed to be continued for a lifetime, each strategy (including diet and exercise) continues to apply these changes throughout the lifetime time horizon. In contrast, the comparison of rimonabant and

sibutramine (based on a 1 year treatment duration) only applies these changes for the first and second years (with the effects reducing linearly in the second year). In subsequent years, patients in both treatments are assumed to revert to their initial 'pre-treatment' baseline risk scores. However, since both treatments as used in addition to diet and exercise, the manufacturer should have assumed that after the first 2 years, patients revert back to the mean risk scores associated with the diet and exercise strategy. By not assuming that patients revert to the same long-term prognosis (and costs) as those on diet and exercise when the treatment duration ends, the manufacturer has underestimated the costs and effects of sibutramine. Consequently, sibutramine appears to be the least effective treatment option because this strategy has been given a prognosis worse than diet and exercise when the 1-year duration (including lag period) is completed.

Given the different assumptions used, the subsequent simultaneous comparison presented by the manufacturer is not considered appropriate by the ERG.

ERG's re-analysis

The ERG has revised the manufacturer's economic model to provide a more appropriate simultaneous lifetime comparison of rimonabant, orlistat, diet and exercise (all lifetime duration) and sibutramine (1-year duration). The ERG altered the structure of the manufacturer's model so that patients in the sibutramine model were assumed to revert to a diet and exercise strategy alone after treatment had been discontinued. The results are presented in Table 6.2 for the same base case populations and sensitivity analysis populations considered by the manufacturer. Diet and exercise is now the least effective (and least costly) treatment option as opposed to sibutramine. The ICER of rimonabant varied between £12,138 and £17,503 per additional QALY across these separate groups.

Table 6.2: Simultaneous comparison of treatment strategies by the ERG

Base case 1: Overweight with treated diabetes

Treatment	Costs	QALYS	ICER
Diet & exercise	£6,779,115	9402.6	-
Sibutramine	£7,347,618	9439.9	ED[1]
Orlistat	£11,012,437	9665.1	ED[2]
Rimonabant	£13,287,230	9894.3	£13,236[3]

1. Ruled out by extended dominance (by orlistat)
2. Ruled out by extended dominance (by rimonabant)
3. ICER vs diet and exercise

Base case 2: Overweight with untreated dyslipidaemia

Treatment	Costs	QALYS	ICER
Diet & exercise	£3,713,588	13564.2	-
Sibutramine	£4,238,166	13611.0	ED[1]
Orlistat	£9,426,205	14142.4	£9,880[2]
Rimonabant	£12,341,535	14382.6	£12,138[3]

1. Ruled out by extended dominance (by orlistat)
2. ICER vs diet and exercise
3. ICER vs orlistat

Sensitivity analysis 1: Overweight with either diabetes or untreated diabetes or obese

Treatment	Costs	QALYS	ICER
Diet & exercise	£4,283,260	12807.6	-
Sibutramine	£4,805,717	12859.0	ED[1]
Orlistat	£9,679,306	13391.4	£9,243[2]
Rimonabant	£12,445,800	13549.4	£17,503[3]

1. Ruled out by extended dominance (by orlistat)
2. ICER vs diet and exercise
3. ICER vs orlistat

Sensitivity analysis 2: Overweight with treated dyslipidaemia

Treatment	Costs	QALYS	ICER
Diet & exercise	£3,504,875	9885.1	-
Sibutramine	£4,015,981	9922.8	£13,534[1]
Orlistat	£7,587,770	10180.0	£13,892[2]
Rimonabant	£9,654,395	10299.5	£17,290[3]

1. ICER vs diet and exercise
2. ICER vs sibutramine
3. ICER vs orlistat

6.3 The absence of response hurdles in the economic model

A major concern for the ERG is the approach to modelling comparators used by the manufacturer in their original submission. As noted in Section 5.4.1, the manufacturer's submission does not consider response hurdles for either orlistat or sibutramine. The manufacturer's approach is, therefore, not in

accordance with the product licences for these drugs or previous NICE guidance on the management of obesity, which specifically recommends continued use on these drugs after 3 months only in people who have lost at least 5% of their initial body weight since starting drug treatment. The ERG requested justification from the manufacturer for excluding strategies involving response hurdles. The ERG also requested additional analyses for the comparator drugs including a 3-month response hurdle.

Manufacturer's response

The manufacturer's clarification regarding their justification for excluding strategies with response hurdles from their original submission states that they consider a robust assessment of such strategies problematic. It reports that to undertake an analysis with sufficient rigour would require access to data that are not available to the manufacturer or in the public domain (i.e. the impact on risk factors conditional upon achieving a 5% weight loss target). The manufacturer emphasises that their submission is focussed on an assessment of long-term cost-effectiveness and, therefore, they consider the comparison of rimonabant to orlistat as therapies that should be considered for use as long-term treatment options.

In response to the ERG's request for additional analyses incorporating alternative strategies for comparator drugs in line with current NICE guidance, the manufacturer presented an additional analysis. Given the concerns raised by the manufacturer in relation to the availability of data, their revised analysis was based on a simplified approach in which response hurdles (5% weight loss) were used to adjust the treatment costs of the different strategies only. The response rates applied in this analysis are reported in Table 6.3. These response rates were used to eliminate treatment-related costs (drug acquisition, monitoring and adverse event costs) after the responder evaluation period of 1 year for rimonabant and diet and exercise, and after 3 months for orlistat and sibutramine, for the proportion of the population who did not achieve ≥ 5% weight loss. Treatment effectiveness estimates were not altered and so the long-term risks and benefits from treatment remained unchanged. The manufacturer stated that this was a conservative approach

because the risk factor changes are based on responders and non-responders, and therefore underestimates the treatment effects in the population that do respond to treatment.

Table 6.3: Response rates applied by the manufacturer

Treatment	Duration	Response rate
Rimonabant	1 year	50.6%
Diet and exercise	1 year	18.5%
Orlistat	12 weeks	33.0%
Sibutramine	12 weeks	25.7%

The estimates of ≥ 5% weight loss at 1 year for rimonabant and diet and exercise were based on pooled results from the four RIO trials. The 12-week response rates for orlistat and sibutramine were obtained using indirect approaches similar to the methods used to derive treatment effectiveness estimates. The difference between orlistat and placebo response rate at 12-weeks was based on an average pooled response rate reported in two studies[51, 54] (18.1%). This was added to the 12-week response rate for people on placebo in the RIO trials (14.9%) to obtain an indirect final estimate of orlistat's 12-week response rate. Similarly for sibutramine, one study[55] was used to inform the difference between sibutramine and placebo response rate at 12-weeks (10.9%), which was then added to the placebo result from the RIO trials to give a final estimate for sibutramine.

The results of the new analyses incorporating the response 'hurdle' are presented in Table 6.4 for the 3 base case populations. The ICER estimates for rimonabant were only marginally higher than those reported for the evaluation without response hurdles and varied between £9,718 and £13,277 per additional QALY.

Table 6.4: Cost-effectiveness results incorporating response hurdles (manufacturer's analysis)

Base case 1: Overweight with treated diabetes				
Treatment	**Costs**	**QALYS**	**ICER**	
Rimonabant - lifetime	£9,651,806	9894.3	£10,741	versus orlistat
Orlistat - lifetime	£7,189,847	9665.1	£6,159	vs diet and exercise
Diet - lifetime	£5,573,263	9402.6	£4,305	versus sibutramine
Sibutramine 1 year	£5,466,631	9377.8	least effective	
Base case 2: Overweight with untreated dyslipidaemia				
Treatment	**Costs**	**QALYS**	**ICER**	
Rimonabant - lifetime	£7,114,849	14382.6	£13,227	versus orlistat
Orlistat - lifetime	£3,938,046	14142.4	£3,572	vs diet and exercise
Diet - lifetime	£1,872,507	13564.2	£306	versus sibutramine
Sibutramine 1 year	£1,776,255	13249.3	least effective	
Base case 3: Obese patients with or without co-morbidities				
Treatment	**Costs**	**QALYS**	**ICER**	
Rimonabant - lifetime	£7,591,624	13954.9	£9,718	versus orlistat
Orlistat - lifetime	£4,565,192	13643.5	£4,516	vs diet and exercise
Diet - lifetime	£2,529,530	13192.7	least effective	

Critique of manufacturer's response

The ERG recognises the concerns raised by the manufacturer in relation to the potential availability of data for the comparator strategies. The ERG also appreciates that to undertake a robust analysis would probably require access to patient-level data for each of the comparators considered. However, the ERG considers that the manufacturer has not attempted to identify this information as part of their submission; it is unclear, therefore, whether there are data in the public domain that could be used for this purpose.

The additional analysis by the manufacturer to address the request to consider alternative strategies for the comparator drugs based on current NICE guidance is limited in a number of aspects.

- Firstly, the manufacturer makes a very simple modification to the model by only adjusting treatment-related costs. Outcomes were assumed to remain the same. This assumption is held across each of the treatment options. The manufacturer states that this is a conservative assumption given that the overall response rate for rimonabant is higher compared to the comparator drugs. They state that by not

applying any increased treatment effect for responders but yet reducing treatment costs by a greater amount for orlistat and sibutramine, the cost-effectiveness estimates for rimonabant are conservative. The ERG does not consider that the adjustment employed by the manufacturer represents a conservative approach, since non-responders still continue to accrue the treatment specific benefits throughout the time horizon of the model. In the absence of estimates of the changes in risk factors for all the treatments, a more conservative approach could be to assume that people who respond only receive the average benefit of treatment and those who don't respond receive the average benefit of diet and exercise.

- Secondly, the manufacturer incorrectly implements the response 'hurdle' by also applying this to the diet and exercise strategy. Consequently, non-responders to diet and exercise are assumed to no longer receive the routine monitoring costs initially assigned to this strategy. A similar issue is noted for the non-responders to the anti-obesity drugs, whereby non-responders no longer receive any monitoring costs. However, since the anti-obesity treatments are given as adjunctive treatments to diet and exercise, the ERG considers it more appropriate for non-responders in all strategies to incur the routine monitoring costs applied to the diet and exercise strategy.

- Thirdly, the ERG is concerned about the lack of transparency in relation to the response rates reported by the manufacturer. These appear to have been derived from recent economic models and no formal searches seem to have been undertaken in relation to the response rate parameters. Consequently, the validity of the estimates presented here is unclear.

ERG's additional analysis

To address some of the concerns above, the ERG conducted an additional analysis using the manufacturer's model. A conservative approach was taken whereby responders to the anti-obesity drugs were assigned the 'average' change in risk factors associated with each treatment and non-responders were assigned the same 'average change' as assumed for the diet and exercise strategy. The ERG also assigned the monitoring costs for diet and exercise to non-responders in subsequent cycles of the model. The results of this re-analysis are presented in Table 6.5.

The re-analysis by the ERG yielded marginally less favourable ICERs than those reported using the manufacturer's approach. However, the ICER for rimonabant remained below £20,000 per QALY across the different populations. These results should be viewed with some caution due to the issues noted regarding the response rates assumed and also the lack of data on the conditional changes in risk factors for each of the individual treatments.

6.4 Uncertainty related to the HRQoL estimates

The final issue considered by the ERG in more detail relates to the HRQoL estimates applied in the model. There are 2 elements considered: (i) the decision to employ external utility estimates as opposed to utilising the HRQoL data reported in the RIO trials; and (ii) the relationship assumed between BMI changes and utility (assumed to result in a 0.014 improvement in utility per point reduction in BMI).

To address the first of these issues, the ERG requested the manufacturer to undertake an additional analysis using the utility data reported in the RIO trials. To address the second issue, the ERG requested additional justification for using HODaR as opposed to external literature estimates to estimate the relationship between BMI and utility. In addition, the ERG requested additional supportive evidence to justify the assumption that a change in health utility of 0.014 per unit change in BMI is comparable to estimates from similar studies in the published literature.

Table 6.5: Cost-effectiveness results incorporating response hurdles (ERG's analysis)

Base case 1: Overweight with treated diabetes

Treatment	Costs	QALYS	ICER
Diet & exercise	£6,779,115	9402.6	-
Sibutramine	£7,031,464	9413.8	ED[1]
Orlistat	£8,243,080	9490.1	ED[2]
Rimonabant	£10,360,830	9664.2	£13,692[3]

1. Ruled out by extended dominance (by orlistat)
2. Ruled out by extended dominance (by rimonabant)
3. ICER vs diet and exercise

Base case 2: Overweight with untreated dyslipidaemia

Treatment	Costs	QALYS	ICER
Diet & exercise	£3,713,588	13564.2	-
Sibutramine	£3,948,617	13578.6	ED[1]
Orlistat	£5,661,165	13756.9	£10,105[2]
Rimonabant	£8,348,083	13995.6	£11,256[3]

1. Ruled out by extended dominance (by orlistat)
2. ICER vs diet and exercise
3. ICER vs orlistat

Base case 3: Obese patients with or without co-morbidities

Treatment	Costs	QALYS	ICER
Diet & exercise	£4,307,632	13192.7	-
Orlistat	£6,204,153	13342.9	ED[1]
Rimonabant	£8,801,383	13594.9	£11,175[2]

1. Ruled out by extended dominance (by rimonabant)
2. ICER vs diet and exercise

Sensitivity analysis 1: Overweight with either diabetes or untreated diabetes or obese

Treatment	Costs	QALYS	ICER
Diet & exercise	£4,283,260	12807.6	-
Sibutramine	£4,517,781	12823.4	ED[1]
Orlistat	£6,126,447	13002.3	£9,467[2]
Rimonabant	£8,681,924	13199.7	£12,946[3]

1. Ruled out by extended dominance (by orlistat)
2. ICER vs diet and exercise
3. ICER vs rimonabant

Sensitivity analysis 2: Overweight with treated dyslipidaemia

Treatment	Costs	QALYS	ICER
Diet & exercise	£3,504,875	9885.1	-
Sibutramine	£3,736,017	9896.5	ED[1]
Orlistat	£4,914,261	9983.8	£14,280[2]
Rimonabant	£6,878,254	10107.6	£15,857[3]

1. Ruled out by extended dominance (by orlistat)
2. ICER vs diet and exercise
3. ICER vs orlistat

Manufacturer's response

As part of their response to the first issue, the manufacturer presented separate analyses using the relationship between BMI change and utility estimated from the RIO trials. Separate analyses were conducted using the relationship estimated using the SF-36 and IWQoL-Lite data, for a comparison between rimonabant and diet and exercise (including a scenario based on the manufacturer's original assumption concerning duration of treatment and a separate scenario employing response hurdles). No comparisons were made against orlisat and sibutramine on the basis that the manufactuer did not consider it appropriate to use RIO-derived data for these comparators. The ICER of rimonabant versus diet and exercise, assuming no response hurdles, is reported for the SF-36 and IWQoL-Lite analyses in Tables 6.6 and 6.7, respectively. In comparison to the base-case analyses, the ICER increases for rimonabant. These varied between £22,035 and £27,144 per additional QALY based on the SF-36 data and £12,574 to £16,125 per additional QALY based on the IWQoL-Lite data. The resulting ICERs from the model employing response hurdles ranged from £7,640 to £16,492 per additional QALY.

Table 6.6: ICER estimates using the SF-36 data

SF-36			
Base case1: Overweight or obese patients with treated type 2 diabetes			
Treatment	**Costs**	**QALYS**	**ICER**
Diet – lifetime	£6,779,115	9236.4	
Rimonabant - lifetime	£13,287,230	9497.3	£24,941
Base case 2: Overweight or obese patients with untreated dyslipidaemia			
Treatment	**Costs**	**QALYS**	**ICER**
Diet – lifetime	£3,713,588	13316.0	
Rimonabant - lifetime	£12,341,535	13633.9	£27,144
Base case 3: Obese patients with or without co-morbidities			
Treatment	**Costs**	**QALYS**	**ICER**
Diet – lifetime	£4,307,632	12915.0	
Rimonabant - lifetime	£12,660,577	13294.1	£22,035

Table 6.7: ICER estimates using the IWQoL-Lite data

IWQoL			
Base case1: Overweight or obese patients with treated type 2 diabetes			
Treatment	**Costs**	**QALYS**	**ICER**
Diet – lifetime	£6,779,115	9489.0	
Rimonabant - lifetime	£13,287,230	9892.6	£16,125
Base case 2: Overweight or obese patients with untreated dyslipidaemia			
Treatment	**Costs**	**QALYS**	**ICER**
Diet – lifetime	£3,713,588	13693.1	
Rimonabant - lifetime	£12,341,535	14379.3	£12,574
Base case 3: Obese patients with or without co-morbidities			
Treatment	**Costs**	**QALYS**	**ICER**
Diet – lifetime	£4,307,632	13337.0	
Rimonabant - lifetime	£12,660,577	13952.1	£13,581

As part of their response to the second issue, the manufacturer reinforced their justification for using HODaR due to the size of the dataset (50,000 patients) and the fact that the dataset allowed for conditioning on a BMI score of >27 kg/m^2. The manufacturer provided additional re-analyses of the relationship based on HODaR without this conditioning which appeared to provide additional supportive evidence that: (i) the relationship appears approximately linear in subjects with a BMI greater than 27, and (ii) the slope coefficient including patients with a BMI <27 will potentially underestimate the relationship. These arguments are then applied to the external estimates provided by the manufacturer, with the manufacturer stating that the published estimates all include subjects with a BMI of less than 27 or consider categorical as opposed to continuous data.

ERG's additional analysis

The ERG has previously outlined that the manufacturer's sensitivity analysis in relation to the impact of BMI on utility resulted in several of the ICER estimates for rimonabant exceeding £20,000 per QALY. The ERG recognises that the assumption employed in this scenario (BMI has no effect) represents a very conservative approach. The ERG was keen, however, to explore other alternative assumptions which lay between the manufacturer's base case assumption (i.e. a change in utility of 0.014 per change in BMI) and the

conservative assumption which assumes no impact. In the absence of a single suitable estimate, the ERG applied an estimate of 0.007 (i.e. half the effect assumed by the manufacturer). This estimate was also applied by the National Centre for Pharmacoeconomics in their review of rimonabant under the community drugs scheme in Ireland.[56] An analysis was therefore conducted by the ERG, based on their revised model employing response hurdles, to illustrate this effect. The ICER for the base-case population considered by the ERG remained below £20,000 per QALY.

Table 6.8: ICER estimates using alternative assumption related to the effect of BMI on utility (0.007)

Base case 1: Overweight with treated diabetes

Treatment	Costs	QALYS	ICER
Diet & exercise	£6,779,115	9368.4	-
Sibutramine	£7,031,464	9377.1	ED[1]
Orlistat	£8,243,080	9434.2	ED[2]
Rimonabant	£10,360,830	9574.1	£17,409[3]

1. Ruled out by extended dominance (by orlistat)
2. Ruled out by extended dominance (by rimonabant)
3. ICER vs diet and exercise

6.5 Uncertainty related to the link between risk factors and events

In Section 5.4.4, the ERG acknowledged that in the absence of direct evidence in relation to the effect of rimonabant on 'hard' clinical endpoints, the approach used by the manufacturer to link individual risk factors to events was appropriate for the purpose of the cost-effectiveness analysis. However, the ERG recognised that the link was subject to considerable uncertainty and that it was difficult to establish from the manufacturer's model the relative importance of the BMI assumptions related to HRQoL and those related to the impact of rimonabant on other events. An exploratory analysis was, therefore, conducted by the ERG, whereby the risk profiles for all treatments (with the exception of BMI) were set to the same level as rimonabant (Table 6.9). The resulting ICER for rimonabant was £31,043 per QALY gained. Although the ERG considers this an exploratory analysis, it does demonstrate that the impact of rimonabant on other risk factors (excluding BMI) and their

subsequent effect on reducing CVD and diabetes events is an important determinant of cost-effectiveness.

Table 6.9: ICER estimates assuming the same risk profile for all treatments (except BMI)

Base case 1: Overweight with treated diabetes

Treatment	Costs	QALYS	ICER
Diet & exercise	£6,929,419	9683.7	-
Sibutramine	£7,178,018	9688.5	ED[1]
Orlistat	£8,413,315	9729.2	ED[2]
Rimonabant	£10,431,192	9796.5	£31,043[3]

1. Ruled out by extended dominance (by orlistat)
2. Ruled out by extended dominance (by rimonabant)
3. ICER vs diet and exercise

7 Discussion

7.1 Summary of clinical effectiveness issues

The data from four clinical trials (the RIO trials) demonstrate that rimonabant is significantly better than placebo, when used in conjunction with diet and exercise. However, the absolute changes in weight over the course of the trials are around 7 kg, average reduction in BMI 1.7 kg/m^2) irrespective of baseline BMI. The long term clinical benefit of rimonabant depends upon its effects on hard cardiovascular outcomes such as myocardial ischaemia and mortality, but no evidence for the effect of rimonabant on these hard outcomes was presented. Data for surrogate outcomes were presented, with no indication of any adverse effect on these cardiovascular risk factors when compared to placebo and some indication of significant beneficial effects. When considering HRQoL, rimonabant did result in significant benefits over placebo, particularly when a specific weight-loss related instrument was used. However, the generic SF-36 identified a significant deterioration in mental health associated with rimonabant. The incidence of psychiatric adverse events is of particular concern. Even though the licence has been revised to preclude its use in patients with ongoing major depressive illness and/or ongoing antidepressive treatment, monitoring for the presentation of symptoms of psychiatric illness may be needed due to the potentially large a

number of patients with depression and other psychiatric disorders that may remain undiagnosed at the time of commencing rimonabant treatment.

A key issue for the effectiveness of rimonabant is the lack of longer-term data. There are no effectiveness or safety data presented for rimonabant beyond 2 years. The limited data (from two trials only) beyond one year indicate slightly less favourable results than those for year 1. Furthermore, trial data have demonstrated that in order that weight loss be maintained, treatment must be continued. In addition, given the concerns regarding psychiatric morbidity, the cumulative data on less common side-effects may be important if rimonabant is to be considered for administered on a longer-term basis. Therefore the effectiveness and safety of rimonabant in the longer-term remains uncertain, and recommendations for its use beyond 2 years would not be evidence-based.

Comparison of the effects of rimonabant on weight loss outcomes with those of orlistat and sibutramine suggest that rimonabant is significantly more effective than orlistat but not sibutramine. There was no comparison of adverse events or HRQoL between rimonabant and orlistat and sibutramine. In addition, there was no comparison of 2 year data between rimonabant and orlistat, despite data being available. In terms of effects on cardiovascular risk factors, apart from the increase in blood pressure in the lipid and diabetic subgroups with sibutramine, there seems to be little difference between rimonabant and orlistat and sibutramine.

The ERG also feels it relevant to draw attention to the difference in the licence of rimonabant compared to orlistat and sibutramine, and therefore the appropriateness of comparators used in their comparison of effectiveness with rimonabant. Both orlistat and sibutramine are subject to response hurdles; in clinical practice, patients who have not achieved a 5% weight loss after 3 months of treatment would no longer be prescribed the drug. Rimonabant is not subject to such restrictions. Therefore, if data from trials of rimonabant prescribed as per licence are compared to data from trials of orlistat and sibutramine where response hurdles have not been applied, any additional

benefit of rimonabant over orlistat or sibutramine may be overestimated, and not be apparent in normal clinical practice. The failure to include a comparison of all response hurdles means that not all relevant comparators will have been considered.

Overall, the ERG found the presentation of the data unclear, particularly that for orlistat and sibutramine. The ERG has doubts over how representative of the general literature the trials of orlistat and sibutramine that are included in the submission are, and how the objectively the data have been used. It is difficult to understand the breakdown of the populations, and how these relate to the base-case analyses used in the economic model. The selection of these studies appears subjective, with inclusion criteria being dictated by those of the RIO trials, rather than the product licences or their use in clinical practice. The confusing presentation of the data and analyses, in conjunction with the discrepancies between the manufacturer's submission and the trial publications in the data extracted for orlistat noted by the ERG, undermines confidence in the review findings.

7.2 Summary of cost effectiveness issues

The manufacturer's submission included a '*de-novo'* decision analytic Markov model to estimate the cost-effectiveness of rimonabant with other licensed anti-obesity drugs (orlistat and sibutramine) and diet and exercise alone. A separate DES model was also presented by the manufacturer. The models were used to evaluate a range of different populations in accordance with the licensed indication for rimonabant. The results from the manufacturers demonstrated that rimonabant appeared cost-effective in each of the main base-case populations and the separate subgroups. These findings were reported to be robust across a wide range of alternative assumptions. The results were most sensitive to the treatment lag assumption applied to the alternative anti-obesity drugs and the assumption relating change in BMI to HRQoL.

The Markov model was submitted to a detailed critique by the ERG. The economic model structure was considered appropriate for the decision problem, and the general approach employed by the manufacturer (in the

absence of long-term event data) of translating changes in intermediate risk factors to changes in event rates were deemed appropriate for the purpose of estimating lifetime cost-effectiveness. However, the ERG identified a number of potential issues related to the manufacturer's economic submission which were considered to compromise the validity of the model results. These included: (i) a lack of simultaneous comparison involving the full range of relevant alternatives; (ii) the absence of response hurdles for orlisat and sibutramine in line with their respective product licences; (iii) the assumption that treatment benefits are maintained in the longer term; (iv) uncertainty surrounding the HRQoL data reported in the RIO trials and the external estimates employed in the model; and (v) uncertainty in relation to the risk equations used.

A number of these issues were addressed by the manufacturer as part of their response to the ERG's points for clarification. The additional analyses presented by the manufacturer demonstrated that rimonabant remained cost-effective when a number of these issues were considered. The ERG identified a number of additional issues related to the manufacturer's response and several of these were addressed through separate analyses conducted by the ERG. The ICER of rimonabant remained relatively robust throughout (<£20,000 per additional QALY), although the ERG noted several important caveats which needed to be considered.

There remain a number of important sources of uncertainty related to the cost-effectiveness of rimonabant. These include the most appropriate way to incorporate response hurdles; the uncertainty surrounding the direct impact of weight loss on CVD and diabetes events; HRQoL benefits of rimonabant and the maintenance of benefits over the longer term.

7.3 Implications for research

In order to allow for an accurate assessment of the clinical and cost-effectiveness of rimonabant in obese and overweight adults there is clearly a need for further research to clarify those areas of uncertainty outlined in this report.

Further research is required in relation to:

- The clinical effectiveness and safety of rimonabant in the long-term
- The short- and long-term effectiveness of rimonabant when response hurdles have been imposed. Outcome data should be collected at several time periods, i.e. 3, 6, 9 and 12 months and at subsequent yearly intervals
- The effect of rimonabant on hard clinical endpoints, such as cardiovascular events, developing diabetes, and mortality
- Establish the link between BMI changes and HRQoL.

Results from the ongoing CRESCENDO trial should inform some of the areas of uncertainty surrounding the effect of rimonabant on cardiovascular morbidity and mortality.

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