

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Rimonabant for the treatment of overweight and obese adults

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

This guidance should be read in conjunction with 'Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children' (NICE clinical guideline 43). In addition, when investigating whether the patient has had a history of depressive disorders/mood alterations, and when monitoring for the emergence of such symptoms, use should be made of the NICE clinical guidelines on the management of anxiety and depression (NICE clinical guidelines 22 and 23), noting the need for careful and comprehensive assessment..

- 1.1 Rimonabant, within its licensed indications, is recommended as an adjunct to diet and exercise for adults who are obese or overweight and who have had an inadequate response to, are intolerant¹ of or are contraindicated to orlistat and sibutramine.
- 1.2 Rimonabant treatment should be continued beyond 6 months only if the person has lost at least 5% of their initial body weight since starting rimonabant treatment.

¹ 'steatorrhoea' as a consequence of not adhering to dietary advice should not be considered as intolerance to orlistat.

- 1.3 Rimonabant treatment should be discontinued if a person returns to their original weight while on rimonabant treatment.
- 1.4 Rimonabant treatment should not be continued for longer than 2 years without a formal clinical assessment and discussion of the individual risks and benefits with the person receiving treatment.

2 The technology

- 2.1 Rimonabant (Acomplia, sanofi-aventis) is a selective cannabinoid 1 (CB1) receptor antagonist. Rimonabant is licensed as an adjunct to diet and exercise for the treatment of obese adults (body mass index [BMI] 30 kg/m² or greater) or overweight adults (BMI greater than 27 kg/m²) with associated risk factor(s) such as type 2 diabetes or dyslipidaemia.
- 2.2 Adverse events associated with rimonabant include nausea, vomiting, diarrhoea, dry mouth, anorexia, depression, anxiety, irritability, nervousness, sleep disorders, and impaired memory and attention. Rimonabant is contraindicated in people with major depressive illness or those receiving concomitant treatment with antidepressants, people with uncontrolled psychiatric illness and people with severe renal impairment. The summary of product characteristics (SPC) states that if depression or psychiatric illness is diagnosed during rimonabant therapy, treatment must be stopped. For full details of adverse events and contraindications, see the SPC.
- 2.3 Rimonabant is licensed at a 20-mg daily dose and is available as 20-mg tablets in a 28-tablet pack. The net price per pack is £44.00 ('British national formulary' [BNF] edition 54). Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of rimonabant and a review of this submission by the Evidence Review Group (ERG; appendix B).

- 3.1 The manufacturer's evaluation of the effectiveness of rimonabant focused primarily on the results of four randomised controlled trials (RCTs) that compared rimonabant with placebo, as an adjunct to diet and exercise (n = 1045, 3045, 1036, and 1507). All four trials assessed outcome measures at 1 year, but only two assessed outcomes at 2 years. Data from three other clinical trials (two unpublished and one published) were also used to inform the analysis of treatment-related side effects. The manufacturer presented the results for people with and without diabetes separately. The RCTs showed that rimonabant, as an adjunct to diet and exercise, was associated with a statistically significant greater weight loss than placebo with diet and exercise at 1 and 2 years. The pooled estimate for the weighted mean difference (WMD) for change in weight from baseline at 1 year was 4.6 kg. At 1 year, rimonabant had a statistically significant beneficial effect on systolic blood pressure (SBP), high density lipoprotein cholesterol (HDL-C), triglycerides and fasting plasma glucose in the diabetic and non-diabetic groups, and glycosylated haemoglobin (HbA1c) in the diabetic group. Improvements in associated cardiovascular and diabetes risk factors were also statistically significantly greater with rimonabant treatment compared with those for placebo at 2 years. However, the relative benefit in terms of weight loss was lower in the second year. After rimonabant treatment was stopped at 1 year, there was a gradual increase in weight until there was no statistically significant difference from placebo at 2 years.
- 3.2 In the RCTs, adverse events were recorded at screening (before treatment and the beginning of the trial) and at visits every

3 months, including an evaluation of mood with the Hospital Anxiety and Depression (HAD) scale. Based on an analysis of the seven studies, the manufacturer reported adverse events in the rimonabant arm with an incidence of equal to or greater than 2%, only when that event was reported by greater than 1% more participants in the rimonabant arm than in the placebo arm (during the first year). These events were nausea, diarrhoea, vomiting, dizziness, anxiety, insomnia, mood alterations with depressive symptoms, depressive disorders, influenza, asthenia/fatigue, gastroenteritis, confusion and hot flushes. During the second year of treatment, the frequencies of the common adverse events in the rimonabant group were generally lower than those observed during the first year, and no new adverse events were noted.

- 3.3 The RCT included two instruments 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 was the generic Medical Outcomes Study Short Form 36 (SF-36). For each instrument the manufacturer presented the individual study results and a pooled analysis. The IWQOL-Lite showed improvements with rimonabant compared with placebo in all domains at 1 year. The SF-36 showed an improvement in physical functioning with rimonabant compared with placebo. However, most of the other SF-36 domains showed a decrease in mean scores for both the rimonabant and placebo groups. The deterioration in the mental health and role-emotional domains was greater for the rimonabant group at 1 year compared with placebo. The deterioration in the bodily pain and general health domains was less for the rimonabant group at 1 year, compared with placebo.
- 3.4 In the absence of head-to-head trials comparing rimonabant with orlistat or sibutramine, the manufacturer compared them indirectly using placebo-subtracted results for orlistat, sibutramine and

rimonabant. The analysis used data from four trials for rimonabant, eight trials for sibutramine and 27 for orlistat. The manufacturer presented results for a pairwise comparison between rimonabant and sibutramine and orlistat. The results showed that for most weight loss outcomes at 1 year, across the three patient populations specified, rimonabant was statistically significantly more effective than orlistat. The only significant difference between sibutramine and rimonabant was the number of people achieving at least 5% weight loss at 1 year in the non-diabetic population, in favour of rimonabant. The manufacturer did not present a comparison of adverse events or HRQoL between rimonabant and orlistat or sibutramine.

3.5 The manufacturer's submission included an economic evaluation of rimonabant based on a Markov model. The model evaluated the following treatment comparisons: lifetime treatment with rimonabant plus diet and exercise versus lifetime diet and exercise alone; lifetime treatment with rimonabant plus diet and exercise versus lifetime orlistat plus diet and exercise; and, 1 year of treatment with rimonabant plus diet and exercise versus 1 year of treatment with sibutramine plus diet and exercise. The results of the economic evaluation were presented for three base-case populations, comprising:

- overweight or obese adults who are being treated for type 2 diabetes; described as the diabetic group
- overweight or obese adults with dyslipidaemia who are not being treated with a statin, and who do not have type 2 diabetes; described as dyslipidaemic group
- obese adults with or without comorbidities (this group was subdivided into adults with diabetes and adults without diabetes); described as the obese group.

Additional subgroups were considered as part of the sensitivity analysis.

- 3.6 The results of pairwise (indirect) comparisons of the effectiveness of rimonabant versus the other anti-obesity drugs were used to obtain estimates of the potential long-term consequences of changes in weight and other risk factors. The data were incorporated into a series of published risk equations to predict the impact of changes in risk factors on the incidence of cardiovascular events or development of diabetes.
- 3.7 Estimates of health-related utility were obtained using the EQ-5D health outcomes instrument. Data on utility values for people without complications (for example, diabetes and coronary heart disease) were based on the 2003 Health Survey for England, and data for people with complications were based on a database of cross-sectional quality of life data. The manufacturer presented sensitivity analyses using the health-related utility data reported in the clinical trials.
- 3.8 Across the base-case populations, the incremental cost-effectiveness ratio (ICER) of rimonabant ranged from approximately £10,500 to £13,200 per additional quality-adjusted life year (QALY) gained versus diet and exercise alone, approximately £9000 to £12,100 per QALY gained versus orlistat and approximately £1500 to £3900 per QALY gained versus sibutramine. In the additional subgroups, none of the individual pairwise ICERs for rimonabant exceeded £20,000 per QALY gained. The ICERs across the majority of the sensitivity analyses were broadly consistent with the base-case results.
- 3.9 The ERG reported that the manufacturer's submission presented a clear overview of the four major trials conducted with rimonabant in overweight or obese adults with data for up to 2 years. The ERG

noted that there is a lack of long-term data on the effectiveness and safety of rimonabant. It also noted that the limited data (from two trials only) beyond 1 year indicated slightly less favourable results than the results presented at 1 year. The ERG reported that the trial data demonstrated that, in order for weight loss to be maintained, treatment with rimonabant would have to be continued.

3.10 The ERG noted the difference in the UK marketing authorisations of rimonabant compared with orlistat and sibutramine. Both orlistat and sibutramine include treatment continuation rules such that people whose weight has not reduced by at least 5% after 3 months of treatment should no longer take the drug. No treatment continuation rules are noted in the marketing authorisation for rimonabant. The ERG highlighted that treatment continuation rules were not reflected for any of the drugs in the manufacturer's economic model. It concluded that the benefit of rimonabant compared with orlistat or sibutramine may be overestimated, and that the analysis did not reflect normal clinical practice.

3.11 The ERG considered that the exclusion/inclusion criteria used to identify the trials of orlistat and sibutramine included in the submission was unclear. Therefore, it could not assess whether the trials were representative of the available data on these treatments. In addition, it was not clear to the ERG which studies were used to derive data for the three separate groups reported, or how the data from the studies contributed to each. Of particular concern was the uncertainty about which studies were used to derive data for the non-diabetic group. It appeared that the data for orlistat and sibutramine reported in the manufacturer's submission were derived from different populations. The data for orlistat were derived from people who were obese with or without dyslipidaemia but without diabetes, whereas data for sibutramine were derived from people who were obese or overweight with dyslipidaemia, and it was unclear to the ERG whether this group included people with

diabetes. It was therefore unclear how this was incorporated into the economic model.

3.12 The ERG considered the economic model structure to be appropriate for the decision problem. In addition, the ERG considered 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 was 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 that it considered compromised the validity of the model results. These included: a lack of simultaneous comparison involving the full range of relevant alternatives; the absence of treatment continuation rules for orlistat and sibutramine in line with their respective UK marketing authorisations; the assumption that treatment benefits are maintained in the longer term; uncertainty surrounding the HRQoL data reported in the clinical trials and the estimates employed in the model; and uncertainty in relation to the risk equations used for predicting events in the long term.

3.13 The Institute asked for clarification on the cost-effectiveness of rimonabant after accounting for the concerns expressed by the ERG relating to: a lack of simultaneous comparison involving the full range of relevant alternatives; the absence of treatment continuation rules for orlistat and sibutramine in line with their UK marketing authorisations and uncertainty surrounding the HRQoL data reported in the clinical trials, and the estimates employed in the model. The ERG also conducted exploratory analyses to reflect treatment continuation rules and different assumptions on the effect of BMI on HRQoL. The ICER of rimonabant remained relatively robust throughout the re-analyses by the manufacturer and the exploratory analysis by the ERG (less than £30,000 per additional QALY gained), although the ERG noted several important caveats

that needed to be considered. These included the most appropriate way to incorporate response hurdles; the uncertainty surrounding the direct impact of weight loss on cardiovascular and diabetes-related events; HRQoL benefits of rimonabant and the maintenance of benefits over the longer term.

3.14 Following a request from the Committee, the manufacturer submitted additional data from the four clinical trials on the health outcomes of adults who responded to treatment with rimonabant (defined as at least 5% weight loss at 3, 6, 9 and 12 months). The manufacturer presented analyses for two populations: overweight or obese people (BMI greater than 27 kg/m²) with diabetes, and obese people (BMI 30 kg/m² or greater) with or without risk factors including diabetes. The analyses included only people who completed weight measurements at 3, 6 and 9 months (completer analysis). Data at 12 months were based on an intention-to-treat analysis, using the last observation carried forward (LOCF) to replace missing data. The manufacturer reported that the odds of achieving at least 5% weight loss at any of the four time points were 3 to 9 times greater in people treated with rimonabant than in people receiving placebo. The manufacturer reported that responders achieved better 1-year weight loss than non-responders and that this improvement was also seen for the majority of the secondary clinical endpoints. The manufacturer stated that the most appropriate time to identify responders and non-responders was at 6 months, because an assessment of response at this time period was a good predictor of response at 1-year. In addition the manufacturer stated that a response hurdle at 6 months was the most clinically appropriate.

3.15 Following a request from the Committee, the manufacturer also revised its estimates of the cost effectiveness of rimonabant compared with diet and exercise alone, with orlistat and with sibutramine. For all treatments the manufacturer included

alternative linear deteriorations in treatment effect and the discontinuation of treatment if the person returns to their original weight. The manufacturer included a continuation rule dependent on the proportion of people on treatment losing 5% of their weight for all treatments. For rimonabant, the manufacturer modelled continuation rules at 3, 6, 9 and 12 months; for orlistat and sibutramine 3-month continuation rules were applied in line with their marketing authorisations. Patient-level data from the trials for rimonabant were used to model responders and non-responders. The clinical data from the orlistat and sibutramine trials were used to model responders and data from diet and exercise trials were used for non-responders. The manufacturer also included a reduction in health-related utility and the costs associated with monitoring depression exclusively for rimonabant.

- 3.16 The manufacturer included treatment deterioration by assuming for rimonabant a linear decline based on data from a trial that was undertaken only in North American centres and a trial undertaken only in European centres. In modelling sibutramine, the manufacturer assumed 1 year of treatment (in line with 'Obesity' [NICE clinical guideline 43]), after which the person returns to diet and exercise alone. For orlistat the manufacturer used data from NICE clinical guideline 43. The same linear deteriorations were applied for all risk factors.
- 3.17 The manufacturer included the impact of depression on HRQoL in the model by applying a decrement of 0.063 derived from a published study that used the EQ-5D instrument. This was applied only to adults treated with rimonabant and at incidence levels based on 1-year trial data. The manufacturer asked clinical specialists to identify the appropriate screening and monitoring approaches and the associated costs. The manufacturer used a two-item questionnaire to screen for depression, in line with 'Depression' (NICE clinical guideline 23). This questionnaire was

assumed to take an additional 1.5 minutes to administer as part of a GP consultation. This would increase the average cost of a GP consultation from £28.60 to £33.12 for rimonabant. The base-case analysis assumed that these additional costs were incurred at the initiation of treatment and every 3 months thereafter.

- 3.18 The manufacturer presented cost-effectiveness results for overweight or obese people with diabetes and obese people with and without risk factors (including diabetes). With a 6-month continuation rule, the ICER for rimonabant compared with diet and exercise was approximately £19,000 per QALY gained in the overweight or obese people with diabetes and approximately £11,900 per QALY gained in people who were obese with and without risk factors. The ICERs for rimonabant compared with orlistat were approximately £28,700 and £23,600 per QALY gained, respectively. The manufacturer was unable to compare rimonabant with sibutramine in people who were obese with and without risk factors because there was a lack of comparable data. The ICER for rimonabant compared with sibutramine in overweight or obese people with diabetes was approximately £30,700.
- 3.19 As part of its response to the ERG request for clarification regarding the potential inconsistency between the approaches used to inform the 3- to 9-month response rates and the 12-month response rates (as described in section 3.15) the manufacturer provided additional cost-effectiveness results using a consistent approach to each time point. The conclusions did not change from the analyses presented in section 3.18.
- 3.20 At the request of the Appraisal Committee, the ERG provided a commentary and validity check on the additional analyses provided by the manufacturer. In general the ERG considered the revised submission provided by the manufacturer adequately addressed the main clarification points raised by the Committee. The ERG

also noted that some of the new assumptions employed by the manufacturer to address these points were conservative with regard to rimonabant. The ERG noted the inconsistency in the approaches used to estimate the response rates for the alternative time points. The ERG considered a full intention-to-treat LOCF would represent a more conservative approach and that the current analyses may overstate the response rates at 3, 6 and 9 months.

- 3.21 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/TAXxx

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of rimonabant for the treatment of overweight and obese adults, having considered evidence on the nature of the condition and the value placed on the benefits of rimonabant by overweight and obese people, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.
- 4.2 The Committee heard from consultees, clinical specialists and patient experts that rimonabant was an important innovation and offered an additional line of treatment for those who were unable to receive treatment with orlistat or sibutramine. The Committee considered the data on the clinical effectiveness of rimonabant as an adjunct to diet and exercise, as reported in the manufacturer's submission. The Committee noted that the majority of people included in the clinical trials were not from the UK. However, it accepted the evidence from the clinical specialists that the populations in the trials were broadly comparable with overweight and obese adults in the UK.

- 4.3 The Committee noted that a continuation rule is specified in the UK marketing authorisations for both orlistat and sibutramine. The Committee heard from the clinical specialists and patient experts that, in clinical practice, a person's response to orlistat or sibutramine is assessed and treatment is continued only if there is a 5% decrease in body weight after 3 months. The clinical specialists stated that the decision to prescribe these therapies for longer than 12 months would be made in consultation with the person after discussing the potential benefits, adverse effects and limitations of continuation. The experts also confirmed that sibutramine is not currently recommended beyond the licensed duration of 12 months. The Committee acknowledged that this practice was consistent with the UK marketing authorisations of the drugs and the recommendations made in 'Obesity' (NICE clinical guideline 43).
- 4.4 The Committee noted that, unlike orlistat and sibutramine, no continuation rule was specified in the UK marketing authorisation for rimonabant. However, the Committee was persuaded by testimony from the clinical specialists and patient experts that, in clinical practice, a person's initial response to rimonabant would always be assessed before deciding whether to continue treatment. The clinical specialists stated that a continuation rule applied after a certain period of time would be an appropriate measure of response to weight-loss therapy. The Committee concluded that treatment with rimonabant could be considered only if appropriate treatment continuation rules were employed and that these should be in accordance with the current guidelines on 'Obesity' (NICE clinical guideline 43) , which suggest a 5% decrease in body weight.
- 4.5 The Committee considered the results of clinical trials that compared rimonabant with placebo, with both used as an adjunct to diet and exercise. It concluded that rimonabant, as an adjunct to

diet and exercise, was more effective at achieving weight loss than diet and exercise alone when assessed at 1 and 2 years after starting treatment. The Committee also acknowledged the importance of adherence to lifestyle changes, including diet and exercise, to achieving and maintaining weight loss. It concluded that participation in lifestyle and diet and exercise programmes was essential in order to achieve long-term weight loss.

4.6 The Committee discussed the adverse effects of rimonabant, especially those linked to alterations in mood and psychiatric symptoms. The clinical specialists highlighted the concerns raised by the European Medicines Agency (EMA) and Endocrinologic and Metabolic Drugs Advisory Committee to the US Food and Drug Administration (FDA) about the safety profile of rimonabant and the lack of safety data on rimonabant beyond 2 years. The Committee understood from clinical specialists and patient experts that the potential that rimonabant has for adversely affecting people's mood was a significant concern, especially given the known association between obesity and depression. The Committee noted that the UK marketing authorisation for rimonabant states that it should not be prescribed to people with uncontrolled psychiatric illnesses and includes a warning that treatment with rimonabant should be stopped if the person develops depression. The Committee agreed with the clinical specialists that people should be assessed for such conditions before treatment with rimonabant is started, and that people should be monitored during treatment for the emergence of signs of depression or other mood disorders.

4.7 The Committee noted that the clinical evidence for rimonabant was based on 1 and 2 years of treatment in the clinical trials. It considered whether the impact of rimonabant on weight loss and biochemical markers for cardiovascular risk, including those relating to diabetes, was likely to be sustained in the long term. The Committee noted that there was evidence from the 2-year trial data

of this effect declining with time. The Committee heard from clinical specialists that although the effects of all weight-loss drugs tend to reduce over time, the initial weight loss and the subsequent delay in weight gain could be valuable for overweight and obese adults in delaying the onset of diabetes and possibly cardiovascular disease.

- 4.8 The Committee considered the recommendations on screening and monitoring for depression in NICE guidelines on anxiety (NICE clinical guideline 22) and depression (NICE clinical guideline 23) and the screening and monitoring undertaken as part of the trials. The Committee noted that the NICE guidelines recommended that screening should include at least the use of the two-item questionnaire, and in the trials the HAD scale was used. The Committee remained concerned that the short questionnaire recommended as a minimum in the guideline may not fully capture the adverse effects of rimonabant on mood. The Committee concluded that screening and monitoring should incorporate both the short questionnaire and more extensive tools for identifying pre-existing depression and assessing and monitoring incidents of depression while receiving treatment with rimonabant.
- 4.9 The Committee carefully considered the analysis provided by the manufacturer that indirectly compared the clinical effectiveness of rimonabant with that of sibutramine and orlistat. The Committee noted the concerns raised by the ERG and some consultees and commentators over the transparency of the selection of trials of orlistat and sibutramine and the data extracted from them. The Committee noted that the selection of trials was the same as that used for a recently published review by the Cochrane Collaboration. The Committee concluded, taking into account evidence from consultees and commentators, that the selection of trials included in the analysis was acceptable. The Committee noted the heterogeneity in the trials included in the analysis and the concerns raised by the ERG about to differences in diet and

exercise that had been employed across the different trials. The Committee considered that the heterogeneity in the trials could lead to bias in the analysis of the comparative clinical effectiveness of these agents, but the direction of the likely bias was not clear. The Committee therefore could not conclude that rimonabant was clinically more or less effective than orlistat or sibutramine.

- 4.10 The Committee discussed the cost effectiveness of rimonabant compared with diet and exercise alone, orlistat and sibutramine. The Committee noted that the manufacturer's revised analysis incorporated treatment continuation rules, costs associated with the monitoring of depression and alternative assumptions about the reduction of treatment effect over time. The Committee noted that the ICERs for rimonabant versus diet and exercise alone varied from £11,600 to £19,000. In comparison with orlistat and sibutramine the ICERs were £30,700 and £28,700 respectively for overweight or obese people. In obese people with or without risk factors the ICER for rimonabant in comparison to orlistat was estimated as £23,600. The Committee noted that the manufacturer had examined only two sets of base-case assumptions in the additional analysis, compared with three in the original. The Committee concluded that the two base cases were representative of those seen in UK clinical practice.
- 4.11 The Committee discussed the key assumptions applied to the economic model. It concluded that the manufacturer's methods for applying the link between BMI and HRQoL, deterioration in treatment effect over time, continuation rules based on 5% weight loss and the discontinuation of treatment when adults have 100% weight regain were acceptable given data limitations. The Committee noted the inconsistency in the manufacturer's approach to response rates for responders and non-responders. It considered the ERG's comment that the use of completer analysis would overestimate the clinical effect of rimonabant. The

Committee concluded that the use of completer analysis instead of LOCF would underestimate the ICERs.

4.12 The Committee considered the use of surrogate measures to link weight loss to long-term cardiovascular and diabetes-related events. The Committee heard from clinical specialists that the link between obesity and diabetes/cardiovascular disease was well established, although the nature of the relationship was difficult to quantify. However, the Committee concluded that, in order to estimate any potential impact of rimonabant on cardiovascular (including diabetes-related) events, it was necessary to extrapolate from surrogate endpoints. The Committee recognised that there was considerable uncertainty in the choice of risk models – especially the Framingham risk equation for cardiovascular disease, which does not reflect recent changes in cardiovascular risk management in the UK and therefore could overestimate the risk of cardiovascular events and the extent to which this is affected by increased BMI.

4.13 The Committee noted that the manufacturer had stated that, because of its mechanism of action, rimonabant might be associated with a reduction in cardiovascular and diabetic events over and above that resulting from the effect on BMI. The Committee considered that obese or overweight people with diabetes or dyslipidaemia would not be treated with an anti-obesity drug alone but would receive treatment with lipid-regulating and/or anti-diabetic drugs. Therefore rimonabant would be comparatively less effective in UK clinical practice. It was aware that the ERG's exploratory analysis in the subgroup of people who were overweight and who are being treated for diabetes demonstrated that removing the additional effect of rimonabant on cardiovascular and diabetes-related events increased the cost-effectiveness estimates from £13,000 to £31,000 per QALY gained compared with diet and exercise alone. The Committee was mindful that there

was no equivalent estimate for the revised analysis, but considered that the removal or reduction of metabolic effects from the analysis could cause the ICERs to be significantly increased. Furthermore, the Committee noted the evidence from the clinical trials, which suggested that weight loss may not be maintained. It considered that short-term weight loss may not have the predicted effect on long-term risk factors as presented in the cost effectiveness analyses. Therefore, the Committee concluded that in the absence of long-term data, such long-term beneficial outcomes could not be assumed to occur and that the ICERs presented by the manufacturer were likely to be significantly underestimated.

4.14 The Committee discussed the estimate of the reduction in health-related utility as a result of depression (-0.063) used in the cost-effectiveness analysis. It noted that the rationale for selecting the data used to inform this estimate was unclear, and noted that alternative data sources were available. The Committee was also aware that the reduction in utility was substantially smaller than that used in previous NICE guidance ('Computerised cognitive behaviour therapy for depression and anxiety'; NICE technology appraisal guidance 97). In addition, the Committee noted that this value did not take into account other associated depressive disorders. The Committee acknowledged that the manufacturer had been conservative by applying the reduction in utility associated with depression over the entire lifetime of a person experiencing depression while on rimonabant treatment, and that this reduction had not been applied to the comparators. The Committee concluded that overall, the effect of depressed mood on quality of life may not be fully reflected in the analysis.

4.15 The Committee noted that the manufacturer's revised estimates of cost effectiveness included some costs associated with screening and monitoring for depression while on treatment with rimonabant.

The Committee considered that the additional costs included in the

analysis may have underestimated the real cost to the NHS. In particular, the Committee considered that the assumption that an additional 1.5 minutes of GP time per consultation would be required was an underestimate of the time required in clinical practice. The Committee considered that this was not sufficient to account for the resources needed for monitoring, particularly given the concerns heard from clinical specialists about the risk of psychiatric morbidity and the fact that some people were likely to present as complex cases. The Committee concluded that the costs associated with both assessment and monitoring in primary care may have been significantly underestimated.

4.16 The Committee noted that the manufacturer's revised estimates of cost effectiveness for rimonabant compared with sibutramine and orlistat were greater than £20,000 per QALY gained. It concluded that some of the assumptions in the model may have led to underestimation of the ICERs, particularly relating to the long-term effect on cardiovascular disease and diabetes and the costs and quality of life associated with treatment-related depression. Therefore the Committee could not recommend rimonabant as an alternative to orlistat and sibutramine.

4.17 The Committee discussed the use of rimonabant as a treatment option for adults who have had an inadequate response to, are unable to tolerate, or have a contraindication to appropriate use of orlistat and sibutramine. The Committee was mindful that there was no evidence presented on the clinical and cost effectiveness of rimonabant in adults who have not had an adequate response to, are intolerant of or have a contraindication to orlistat and sibutramine. The Committee further emphasised the importance of appropriate interpretation of 'intolerance' in the context of orlistat therapy, noting that steatorrhoea as a consequence of not adhering to appropriate dietary advice (as recommended in section 4.2 of the SmPC for orlistat) should not be considered as an intolerance to

orlistat. The Committee concluded that the appropriate comparator was diet plus exercise alone. The Committee noted that the ICER for rimonabant versus diet and exercise was below £20,000. The Committee was mindful of the possibility that the ICER may be higher, given the concerns described above, but concluded that the ICER was unlikely to increase beyond that considered to be a reasonable use of NHS resources. The Committee also considered the lack of alternative options in this group of people for whom other treatments have failed. It concluded that rimonabant is a cost-effective option for adults who have had an inadequate response to, are unable to tolerate or have a contraindication to orlistat and sibutramine.

- 4.18 The Committee considered the analysis of treatment continuation rules for rimonabant. It noted that guidance on the use of orlistat and sibutramine recommends that weight loss and the need for continued treatment should both be assessed at 3 months. However, the Committee accepted that the data for rimonabant showed that response to treatment with rimonabant is more appropriately assessed at 6 months than at 3 months. The Committee concluded that people treated with rimonabant should be assessed for response at 6 months, treatment continued only if the person has achieved a weight loss of 5% or more of their original body weight and discontinued if a person returns to their original weight while on treatment.
- 4.19 The Committee considered the issues raised about the lack of long-term clinical effectiveness data for rimonabant and the safety concerns beyond 2 years. The Committee concluded that treatment with rimonabant should continue for no longer than 2 years without a formal clinical assessment and discussion of the individual risks and benefits with the person being treated.

5 Implementation

- 5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.
- 5.2 'Healthcare standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 that requires local health boards and NHS trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.
- 5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TAXXX). [NICE to amend list as needed at time of publication]
- Slides highlighting key messages for local discussion.
 - Costing report and costing template to estimate the savings and costs associated with implementation.
 - Implementation advice on how to put the guidance into practice and national initiatives that support this locally.

- Audit support for monitoring local practice.

6 Recommendations for further research

6.1 Further research is recommended to assess:

- the long-term clinical effectiveness and safety of rimonabant
- the short- and long-term effectiveness of rimonabant if continuation rules are imposed.
- the effect of rimonabant on hard clinical endpoints, such as cardiovascular events, the development of diabetes and mortality
- the link between BMI changes and HRQoL
- the effectiveness of rimonabant in adults who have had an inadequate response to, are unable to tolerate or have a contraindication to orlistat and sibutramine.

7 Related NICE guidance

- Behaviour change at population, community and individual levels. NICE public health guidance 6 (2007). Available from www.nice.org.uk/PH006
- Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children. NICE clinical guideline 43 (2006). Available from www.nice.org.uk/CG043
- Anxiety: management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care. NICE clinical guideline 22 (2004). Available from www.nice.org.uk/CG022
- Depression: management of depression in primary and secondary care. NICE clinical guideline 22 (2004). Available from www.nice.org.uk/CG023

- Four commonly used methods to increase physical activity: brief interventions in primary care, exercise referral schemes, pedometers and community-based exercise programmes for walking and cycling. NICE public health intervention guidance 2 (2006). Available from www.nice.org.uk/PHI002

8 Review of guidance

- 8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.
- 8.2 The guidance on this technology will be considered for review in April 2010, to incorporate new information from clinical trials of rimonabant in patients with diabetes and cardiovascular disease.

Ken Stein

Vice Chair, Appraisal Committee

March 2008

Appendix A: Appraisal Committee members, guideline representatives and NICE project team

A *Appraisal Committee members*

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice chair. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jeff Aronson

Reader in Clinical Pharmacology, Radcliffe Infirmary, University of Oxford

Dr Darren Ashcroft

Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Professor David Barnett

Professor of Clinical Pharmacology, University of Leicester

Professor John Cairns

Public Health and Policy, London School of Hygiene and Tropical Medicine

Dr Mark Charkravarty

Head of Government Affairs and NHS Policy, Procter and Gamble
Pharmaceuticals (UK)

Ms Lynn Field

Nurse Director, Pan Birmingham Cancer Network

Professor Christopher Fowler

Professor of Surgical Education, University of London

Dr Fergus Gleeson

Consultant Radiologist, Churchill Hospital, Oxford

Ms Sally Gooch

Former Director of Nursing & Workforce Development, Mid Essex Hospitals
Services NHS Trust

Mr Sanjay Gupta

Former Service Manager in Stroke, Gastroenterology, Diabetes and
Endocrinology, Basildon and Thurrock University Hospitals Foundation NHS
Trust

Mr Terence Lewis

Mental Health Consultant, National Institute for Mental Health in England

Professor Gary McVeigh

Professor of Cardiovascular Medicine, Queens University, Belfast

Dr Ruairidh Milne

Senior Lecturer in Health Technology Assessment, National Coordinating
Centre for Health Technology

Dr Neil Milner

General Medical Practitioner, Sheffield

Dr Rubin Minhas

General Practitioner, CHD Clinical Lead, Medway PCT

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Rosalind Ramsay

Consultant Psychiatrist, Adult Health Services, Maudsley Hospital, London

Dr Lindsay Smith

General Practitioner, East Somerset Research Consortium

Mr Cliff Snelling

Lay member

Professor Ken Stein (Vice Chair)

Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Dr Rod Taylor

Associate Professor in Health Services Research, Peninsula Medical School, Universities of Exeter and Plymouth.

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Nicola Hay and Prashanth Kandaswamy

Technical Leads

Dr Louise Longworth

Technical Adviser

Natalie Bemrose

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by NHS Centre for Reviews and Dissemination and Centre for Health Economics, York:

- McKenna C, Palmer S, Sculpher M, et al. Rimonabant for the treatment of overweight and obese patients the Evidence Review Group's report, October 2007.

B The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II gave their expert views on rimonabant by providing a written statement to the Committee. Organisations listed in I and II have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- sanofi-aventis

II Professional/specialist and patient/carer groups:

- Action Heart
- Association of British Clinical Diabetologists
- British Heart Foundation
- British Obesity Surgery Patient Association
- Department of Health
- Diabetes UK
- Faculty of Public Health Medicine
- Heart UK
- Obesity Awareness and Solutions Trust (TOAST)
- Primary Care Cardiovascular Society
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Physicians
- Royal Pharmaceutical Society
- Society for Endocrinology
- South Asian Health Foundation
- The Obesity Management Association

- Weight Concern
- Welsh Assembly Government

III Commentator organisations (did not provide written evidence and without the right of appeal):

- Abbott Laboratories
- Department of Health, Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland
- Roche Products

C The following people were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on rimonabant by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Nicholas Finer, Consultant in Obesity Medicine, nominated by Association of British Clinical Diabetologists – clinical specialist
- Professor John Wilding, Professor of Medicine, nominated by Association of British Clinical Diabetologists – clinical specialist
- Tam Fry, Chairman Child Growth Foundation, nominated by Child Growth Foundation – patient expert
- Dr Colin Waite, Chairman National Obesity Forum, nominated by National Obesity Forum – patient expert