A systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity

Report commissioned by the NHS R&D HTA Programme on behalf of The National Institute for Clinical Excellence (NICE)

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Date completed 7th December 2000

Expiry date: November 2001

[Commercial in confidence material provided by the manufacturer has been omitted from this report in the places indicated in the text. Page numbering has also changed a little as a result of the removal of text.]

Source of funding

This report was commissioned by the NHS R&D HTA Programme.

Acknowledgements

The review team wish to thank the expert advisory panel for their useful and constructive comments on the review protocol and draft report (appendix 1). We are also most grateful to Julie Glanville, Information Manager at NHS CRD, for assistance with contacting authors of conference abstracts, and to Caroline Horwood and Vanda Castle for secretarial support.

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Executive summary

Background

The prevalence of obesity in developed societies is increasing. Obesity is associated with an increased risk of co-morbidity including cardiovascular disease and diabetes. Following the withdrawal of fenfluramine and dexfenfluramine interest has focused on a novel antiobesity drug: orlistat.

Aims of the review

To systematically assess the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity.

Methods

Search strategy

Nineteen electronic databases were searched from inception to June 2000. Additionally, internet searches were carried out, bibliographies of retrieved articles were examined, and submissions were received from drug companies.

Inclusion and exclusion criteria

RCTs evaluating the effectiveness of orlistat used for weight loss or maintenance of weight loss in overweight or obese patients were eligible for inclusion. Primary outcome measures were changes in body weight, fat content, or fat distribution. Secondary outcomes were changes in obesity-related risk factor profiles, such as lipid levels, indicators of glycaemic control, and blood pressure. Studies recruiting people with eating disorders such as anorexia nervosa and bulimia nervosa were excluded.

Process of study selection

Assessment of titles and abstracts was performed independently by two reviewers. If either reviewer considered a reference to be relevant, the full paper was retrieved. Full papers were assessed against the review selection criteria by two independent reviewers. Disagreements were resolved through discussion.

Data extraction

Data were extracted by one reviewer into structured summary tables, and checked by a second reviewer. Any disagreements about data were resolved by discussion.

Quality assessment

Each included trial was assessed against a comprehensive checklist for methodological quality. Quality assessment was performed independently by two reviewers with disagreements resolved by discussion.

Methods of analysis / synthesis

A narrative summary is presented, with results grouped according to drug and study endpoint. Statistical pooling was undertaken in groups of trials that were considered to be sufficiently similar.

Estimation of quality of life, costs and cost-effectiveness and/or cost/QALY

Relevant economic evaluations were identified from the search strategy described above. Assessment of methodological quality was undertaken using principles outlined in published guidelines.

Company submissions

Data from company submissions were subject to the same selection and appraisal processes as other studies considered for inclusion in the review, with the exception that only RCTs with a duration of at least one year were selected.

Results

Results of search strategy

Fourteen RCTs and two economic evaluations were included in the review.

Results of quality assessment

Methodological quality of trials was moderate to good. The main problems were lack of detail on methods to produce true randomisation, small sample sizes in some cases, and failure to use intention-to-treat analysis. It is likely that maintenance of blinding was difficult due to adverse effects associated with the study medication.

Results for clinical effectiveness and cost-effectiveness

Most of the trials showed greater weight loss, and better weight maintenance in orlistat groups versus placebo, at all endpoints (statistically significant differences for both outcomes). Orlistat 120 mg three times per day was the optimum regimen in terms of weight loss. Most trials showed significant improvement in at least some lipid concentration parameters, and in three RCTs, orlistat produced statistically significant reductions in blood pressure relative to placebo. In obese patients with type-2 diabetes, orlistat produced statistically significant greater weight loss at one year compared with placebo, and some parameters of glycaemic control and lipid concentration also showed statistically significant greater improvement compared with placebo. The incidence of gastrointestinal adverse events was consistently higher in orlistat groups compared with placebo, and orlistat use was associated with lower serum levels of fat-soluble vitamins. Two economic evaluations were identified that generated differing values for cost per QALY (£10,433 and £45,881), however, the lower figure was based on an assumption for weight loss that may be inaccurate.

Conclusions

Implications for future research

Future trials should ensure good methodological quality. Further research is required to determine the effects of orlistat in different patient groups according to gender, age, ethnicity and social class. Clinical trials should be designed to match protocols observed in clinical practice with regard to patient selection and treatment.

Implications for clinical practice

Although many trials demonstrated statistically significant differences between groups in terms of weight loss in favour of orlistat versus placebo, the differences may not always be of clinical significance. The clinical significance of between-group differences for secondary outcomes may also be debatable. Possible adverse effects should be taken into account when prescribing orlistat, particularly gastrointestinal effects.

List of abbreviations

ANCOVA	analysis of covariance
ANOVA	analysis of variance
BMI	body mass index
CHD	coronary heart disease
CVD	cardiovascular disease
DBP	diastolic blood pressure
DEC	Development and Evaluation Committee
EMEA	European Agency for the Evaluation of Medicinal Products
FDA	Food and Drug Administration
HDL-C	high-density lipoprotein cholesterol
LDL-C	low-density lipoprotein cholesterol
LOCF	last observation carried forward
LYG	Life Years Gained
OHE	Office of Health Economics
QALY	quality adjusted life year
QoL	quality of life
RCP	Royal College of Physicians
RCT	randomised controlled trial
RR	relative risk
SBP	systolic blood pressure
SIGN	Scottish Intercollegiate Guidelines Network
Tid	three times per day
TTO	time-trade-off
VAS	visual analogue scale
VLDL-C	very-low-density lipoprotein cholesterol
WHO	World Health Organisation
WMD	weighted mean difference
95% CI	95% confidence intervals

Background

The prevalence of obesity

Epidemiological surveys in England indicate that the prevalence of obesity, defined as a body mass index (BMI) of greater than 30 kg/m^2,[1] is increasing.[2-4] In 1994, it was estimated that, for those aged over 16 years, 44% of men were classified as overweight (BMI >25 - 30 kg/m^2), and 13% were classified as obese (BMI >30 kg/m^2). For women the figures were 31% and 16% respectively. In 1998, the respective figures had risen to 46% and 17% in men, and 32% and 21% in women.[4] Projected figures for prevalence (both sexes) in the year 2000 are 50% for overweight and 20% for obesity.[5]

Those at risk of becoming obese

It is deemed that large sections of the population in developed societies are at risk of developing obesity.[6] Those considered to be particularly at risk include Asian people,[7] children from families where one or both parents are overweight or obese,[8-10] and those giving up smoking.[11] High birth weight may also be associated with an increased risk of obesity later in life.[10]

The risk of obesity is associated with social class (defined as social class of head of household) and household income. In 1998 it was estimated that 14% of women in social class I were obese, compared with 18% in social class III (non-manual) and 28% in social class V. However, the pattern of association was less clear for overweight women, and for obese and overweight men. In terms of household income, the prevalence of obesity in both sexes decreases as income increases. However, the relationship between income and being overweight in both sexes is less clear. These data are age-standardised.[4] Findings from a systematic review of childhood predictors of adult obesity showed that there is a link between low socio-economic status in early life and obesity in adulthood.[10]

The risk of becoming obese increases with age, up to a certain point, in both sexes. In 1998, it was estimated that 16% of men aged between 25 and 34 years were obese

(BMI greater than 30 kg/m^2), compared with 23% aged between 55 and 64 years. For women, the respective figures were 16% and 29%. It should be noted, however, that the BMI tends to decrease in older people. This decline begins between 65 and 74 years in men, and from 75 years onwards in women.[4] It is also thought that men and women are at greater risk of becoming obese at certain points in the life cycle, with an increased risk for men during the late 30s. Women may be more vulnerable when entering marriage, during pregnancy, during the menopause, and at retirement.[1]

Health risks of obesity

These include increased risk of coronary heart disease, hyperlipidaemia, hypertension, diabetes, cholelithiasis, degenerative joint disease, social and psychological problems,[12] and obstructive sleep apnoea.[13-16] More specifically, there is a link between android or abdominal obesity and coronary heart disease, hypercholesterolaemia, hypertension, and diabetes.[17-19]

It has been suggested that even modest reductions in weight may be associated with health benefits, with reductions in blood pressure, cholesterol, and triglycerides achievable with just a 5-10% reduction in initial body weight.[20] In order to obtain long-term health benefits, however, weight loss must be maintained. Concern has been expressed over weight cycling (or 'yo-yo dieting') whereby some individuals alternate between periods of weight loss and weight regain. However, the association between weight cycling and morbidity remains unclear.[21-25]

Measurements of obesity

Definitions of the terms 'overweight' and 'obesity' vary between studies. The Body Mass Index (BMI) (body weight in kilograms divided by the height in metres squared) is frequently used as a method of classification in research, clinical practice, and public health settings (see below). However, the BMI does not take into account factors such as size of body frame, proportion of lean mass, gender and age. Measures of central obesity, such as waist circumference, are considered to be better predictors of cardiovascular risk.[17] Other measurements include body weight, percentage over ideal body weight, skinfold thickness and other more details measures of body composition such as densitometry.

Classification of weight according to BMI level:[26]

WHO classification	BMI (kg/m^2)	Risk of co-morbidities
Underweight	<18.5	Low (but risk of other clinical problems increased)
Normal range	18.5-24.9	Average
Overweight	25.0-29.9	Mildly increased
Obese	≥30.0	
Class I	30.0-34.9	Moderate
Class II	35.0-39.9	Severe
Class III	≥40.0	Very severe

Options for the management of obesity

A range of interventions are available for the management of overweight and obesity. These include work/school/community programmes (for primary prevention), dietary modification, exercise programmes, behaviour modification programmes, pharmacological agents, commercial programmes (e.g. Weight Watchers), and alternative therapies. Surgery is usually reserved for those suffering from very severe obesity (BMI greater than 40 kg/m^2), for whom less invasive methods of weight loss have failed. The various weight management strategies may be used alone or in combination. A number of literature reviews have covered the broad range of interventions available,[27-30] and recent reports have offered guidelines for the management of obesity.[28, 31]

Pharmacological agents used to treat obesity

In 1997, dexfenfluramine and fenfluramine were withdrawn by the manufacturer due to reported cases of valvular heart disease. Following this event, interest in a novel anti-obesity agent, orlistat, was intensified.

Orlistat

Orlistat (Xenical®) is produced by Roche Products Limited, Welwyn Garden City, UK. The parent company is Hoffmann-La Roche. It has been licensed in the UK since September 1998 as an anti-obesity drug. It was approved by the FDA in April 1999. Orlistat is an inhibitor of gastric and pancreatic lipases. It inhibits the hydrolysis of dietary triglycerides, consequently limiting the absorption of monoglycerides and free fatty acids. Orlistat is indicated for patients with a BMI of

30 kg/m^2 or more, or 28 kg/m^2 or more in the presence of other risk factors (e.g., hypertension, diabetes, hyperlipidaemia).[32]

Orlistat is contraindicated in patients with chronic malabsorption syndrome or cholestasis, in pregnancy or while breastfeeding, and in patients with known hypersensitivity to orlistat or to any component of this product. Adverse effects include liquid oily stools, faecal urgency, flatulence, and less frequently, abdominal and rectal pain, headache, menstrual irregularities, anxiety and fatigue.[32]

Orlistat is licensed for use with a mildly hypocaloric diet.[32] Prescribing guidelines indicate that treatment with orlistat should only be initiated in patients who have achieved a weight loss of at least 2.5 kg in four weeks using a dietary programme alone.[32, 33] It is also recommended that orlistat treatment should be discontinued after 12 weeks in patients who lose less than 5% of their initial body weight.[33] European prescribing guidelines also reflect these recommendations and state that the duration of treatment with orlistat should not be longer than two years.[34]

Other drugs

Sibutramine (Meridia®) is produced by Knoll Pharmaceutical Company. BASF Pharma is the parent company. It is not yet licensed for any use in the UK, but was approved by the Food and Drug Administration (FDA) in the USA in November 1997 for the treatment of obesity. It is a dopamine, norepinephrine, and serotonin reuptake inhibitor, and also stimulates thermogenesis, thus increasing energy expenditure. Sibutramine is indicated in the management of patients with a BMI of 30 kg/m^2 or more, or in those with a BMI of 27 kg/m^2 or more in the presence of other risk factors (i.e. hypertension, diabetes, hyperlipidaemia).

Sibutramine increases blood pressure in some patients, therefore regular monitoring is required. It is contraindicated in the following: those receiving monoamine oxidase inhibitors (MAOIs), patients with hypersensitivity to sibutramine or any of the inactive ingredients of sibutramine, sufferers of anorexia nervosa, and those taking other centrally acting appetite suppressants.

More frequent adverse effects include dry mouth, anorexia, insomnia and constipation. Other potential adverse effects are fever, diarrhoea, flatulence, gastroenteritis, tooth disorders, peripheral oedema, arthritis, agitation, leg cramps, hypertonia, abnormal thinking, bronchitis, dyspnoea, pruritus, amblyopia, menstrual disorders, seizures, ecchymosis bleeding disorders, and interstitial nephritis.

This information about sibutramine was obtained from RxList (http://www.rxlist.com) on 26th June 2000.

In addition to orlistat, two other drugs are currently licensed in the UK for the treatment of obesity.[32] One of these is the bulk-forming agent methylcellulose (Celevac® Monmouth, UK), which is deemed to reduce food intake by producing a feeling of satiety. However, there is little evidence to support this claim.[35] Patients taking this drug must be advised to maintain an adequate fluid intake. Contraindications to use are gastrointestinal obstruction. Adverse effects include flatulence, abdominal distension, and gastrointestinal obstruction.

The second drug is phentermine (Duromine® 3M, Ionamin® CHS) a catecholaminergic drug with sympathomimetic and stimulant effects. It is licensed for use as an adjunct to the treatment of selected patients with moderate to severe obesity, with prescription restricted to 12 weeks or less. Phentermine is associated with the rare but serious risk of pulmonary hypertension which may be insidious, as well as a number of less serious adverse effects. Cautions include mild hypertension (avoid if moderate or severe), diabetes mellitus, and a history of anxiety or depression. Associated contraindications are cardiovascular disease, glaucoma, hyperthyroidism, epilepsy, unstable personality, history of psychiatric illness, history of drug/alcohol abuse, pregnancy, and breastfeeding.

This review will not assess the effectiveness of methylcellulose or phentermine. The clinical effectiveness and cost-effectiveness of sibutramine will be considered in a separate report.

It is generally agreed that pharmacological agents are unsuitable for use as a sole treatment but rather should be employed as an adjunct to other weight-loss interventions such as prescribed diet, exercise, or behavioural therapy. Published guidelines for the management of obesity from the Royal College of Physicians (RCP) and the Scottish Intercollegiate Guidelines Network (SIGN) endorse this view,[28, 31] as do prescribing guidelines.[32] Further recommendations from the RCP state that anti-obesity drugs should not be prescribed for longer than 12 weeks initially. After this time, weight loss should be assessed, and therapy should be discontinued in patients who have not achieved at least 5% reduction of initial weight. Prescription may be continued beyond this period for patients attaining at least 5% loss of initial body weight, provided body weight is continually monitored and weight is not regained.[31]

At present, drugs are not normally used for childhood obesity because of the risks of growth suppression. Most of the research literature has so far reflected their use in adults aged up to 75 years.[27]

Aim of the review

To assess systematically the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity. In this context, the term 'management' covers both weight loss and weight maintenance programmes. The review will consider both overweight and obese people. The main outcomes of interest will be those reflecting changes in body weight, fat content, or fat distribution. Other relevant health-related outcomes will also be considered.

Methods

Search strategy

The following electronic databases were searched from inception to the end of June 2000 to locate information on the clinical effectiveness and cost-effectiveness of orlistat (using both generic and brand names) in the treatment of obesity:

Allied and Complementary Medicine database (AMED)

BIOSIS

British Nursing Index

Cochrane Library CD-ROM (2000 issue 2)

Cumulative Index to Nursing and Allied Health Literature (CINAHL)

Database of Abstracts of Reviews of Effectiveness (DARE)

DH-Data

EconLit

EMBASE

Health Management Information Service database (HELMIS)

HTA database

Index to Scientific and Technical Proceedings

King's Fund Database

MEDLINE

National Research Register (NRR) (2000 issue 1)

NHS Economic Evaluation Database (NHS EED)

OHE Health Economic Evaluations Database (HEED)

Science Citation Index

Social Science Citation Index

The search strategy used is provided in Appendix 2.

In addition, searches were carried out on the Internet using the Hoffmann-La Roche website, pharmaceutical databases such as PharmInfo Net (http://www.pharminfo.com/) and RxList (http://www.rxlist.com), biomedical search engines such as OMNI (http://www.omni.ac.uk), meta-search engines such as The BigHub.com (http://www.thebighub.com/) and general search engines such as AltaVista (http://www.altavista.com/).

The reference lists of relevant reviews and included trials were checked in order to identify further eligible evaluations. When relevant conference abstracts were identified, authors were contacted and requested to provide a full report (for trials) or a bibliography (for reviews).

In addition to the above, material was submitted from the manufacturers of orlistat.

Inclusion and exclusion criteria

In order to be included in the review, studies had to fulfil criteria relating to study design, participant characteristics, interventions, and outcomes.

1. Study design

Randomised controlled trials (RCTs), incorporating any duration of therapy and any length of follow-up, were considered for inclusion in the review.

2. Participants

The following were included in the review:

a. RCTs recruiting participants defined as being overweight or obese.

b. RCTs recruiting participants wishing to maintain weight loss, having been previously overweight or obese.

Trials involving specific patient groups such as those with diabetes, hypertension, or hyperlipidaemia, were included in the review, provided they met the above criteria.

Definitions of obesity and being overweight vary between studies. Studies recruiting participants who were not overweight or obese who wished to achieve weight loss were excluded. Evaluations for which mixed participants were recruited (e.g. some with healthy weight, some overweight / obese) were included if results were presented separately for the overweight / obese patients.

Studies recruiting people with eating disorders such as anorexia nervosa and bulimia nervosa were excluded. In trials where overweight / obese participants were recruited as well as those with the above eating disorders, only those where results were presented separately for the overweight / obese participants were included.

3. Interventions

Evaluations of orlistat used to treat overweight / obese patients, or maintain weight loss in previously overweight / obese patients were considered for inclusion in the review. Orlistat could be combined with other strategies such as dietary restriction, or behavioural programmes. Participants in control groups could receive placebo, an alternative anti-obesity pharmacological agent, or an alternative anti-obesity intervention (e.g. based on dietary regimen, physical activity, or behavioural modification).

4. Outcomes

The primary outcome of the review was an assessment of obesity / overweight status measured as changes in body weight, fat content, or fat distribution (see below). In order to be included, trials had to report measurements at baseline and post-intervention.

a. Measures of weight change include absolute weight change and percentage weight change relative to baseline.
b. Measures of fat content include Body Mass Index (BMI), ponderal index, skin fold thickness, fat free mass, and fat change.
c. Measures of fat distribution include waist size, waist-hip ratio, and girth-height ratio.

Secondary outcomes of the review included physiological changes occurring in association with changes in body weight / fat content / fat distribution. The most common examples of these were changes in lipid profiles, glycaemic control among those with diabetes, and blood pressure among those with hypertension. Where available, data were recorded on patient-related quality of life.

Data on adverse effects and costs were also recorded, where available.

5. Language restrictions

Only studies published in English, French, Dutch, or German were considered for inclusion in the review.

Process of study selection

All titles and abstracts were assessed independently by two reviewers. If either reviewer considered a reference to be potentially relevant, a hard copy of the paper was retrieved for further consideration.

Full papers were assessed against the selection criteria detailed above (see prescreen form, Appendix 3). Prescreening was performed independently by two reviewers. Disagreements were resolved through discussion or by recourse to a third reviewer.

Data extraction

The following data were extracted from each included trial: authors' name(s), year of publication, country of study, study aim, method of randomisation, outcomes measured, setting of treatment, duration of treatment and follow-up, participant selection criteria, baseline comparability of groups, intervention characteristics, results per treatment arm, incidence of adverse effects, and numbers of/reasons for withdrawal. Data were extracted by one reviewer into standardised, structured tables, (see Appendix 4), and were checked by a second reviewer. Any disagreements about data were resolved through discussion. Where multiple publications of the same evaluation were identified, all publications were examined to ensure that all relevant data for that study were recorded, and data were presented as a single study.

Quality assessment

Each included trial was assessed against a comprehensive checklist for methodological quality. The following aspects of quality were assessed: method of randomisation, participant selection criteria, sample size, comparability of treatment arms, blinding, statistical analysis, and description of withdrawals (Appendix 5). Quality assessment was performed independently by two reviewers with disagreements resolved through discussion.

Methods of analysis / synthesis

A narrative summary of results has been presented, with results grouped according to study endpoint and type of weight management programme (weight loss or weight maintenance). Statistical pooling (meta-analysis) has been undertaken for groups of

trials that were considered to be sufficiently similar. For continuous data, a pooled weighted mean difference (WMD) was generated, and for dichotomous variables, a summary relative risk (RR) was calculated. The summary RR was calculated in terms of the risk of failure to achieve 5% or 10% loss of initial body weight. A random effects model was employed for both types of analyses, and 95% confidence intervals (95% CI) were presented with the central effect estimates. The results of related statistical tests for heterogeneity have been presented with each analysis. Statistically significant heterogeneity was considered to be present when the associated p-value was less than 0.10. The meta-analyses were generated using Metaview 4.1 (Review Manager 4.1, 2000 The Cochrane Collaboration).

Estimation of quality of life, costs and cost-effectiveness and/or cost/QALY

The following specialist sources were searched to identify relevant economic literature: EconLit, NHS Economic Evaluation Database (NHS EED), and the Office of Health Economics (OHE) Health Economic Evaluations Database (HEED). Identified economic evaluations were submitted to the same review process as studies of clinical effectiveness relating to study selection and data-extraction. Assessment of methodological quality was undertaken using principles outlined in published guidelines.[36] Data extraction tables and quality assessment tables for economic evaluations are shown in Appendix 6 and Appendix 7 respectively.

Company submissions

Data from company submissions were subject to the same selection and appraisal processes as other studies considered for inclusion in the review. The sole exception to this was that, for company submissions, only RCTs with a duration of at least one year were selected. This post-hoc decision was taken in light of the time constraints of this review. Sections of this report containing confidential information have been indicated by underlining. In accordance with instructions from NICE / NCCHTA, confidential data from company submissions were not included in the draft document that was circulated for review by the expert panel.

Results

Results of search strategy

The search strategy (see above and appendix 2) generated 658 references of possible relevance to this review. Once titles (and where available, abstracts) had been assessed, hard copies of 187 papers were examined (please note that these figures relate to the joint review of the two drugs orlistat and sibutramine). Fourteen RCTs of orlistat were included,[37-50] and two economic evaluations.[51, 52] Details of included trials are summarised in appendix 4 (appendix 6 for economic evaluations).

Quality assessment of RCTs

Eleven published trials of orlistat were included.[37-47] One trial reported the use of procedures to produce true randomisation,[40] in one it was unclear,[43] and in all other trials it was not stated. All trials used concealment of randomisation (assumed from description of 'double-blind'), but methods used to achieve concealment were not described. All trials reported participant selection criteria. Two trials provided details of an *a priori* power calculation for sample size.[40, 43] Two trials allocated between 20 and 50 participants per group,[37, 38] one trial recruited 60 participants per group,[45] and eight trials recruited over 100 patients per group.[39-44, 46, 47] All reported baseline comparability of treatment groups, indicated intention to provide identical treatment to patients apart from the drugs under study, and blinded patients. In all cases, it was unclear whether care-givers were blinded, although all the trials were described as 'double-blind'. The same was true for blinding of outcome-assessors, except in one trial where it was stated that they were blind.[43] None of the trials reported assessment of blinding of patients, care-givers, or outcome-assessors. All trials described statistical methods used, but three did not provide variance around central estimates.[39, 43, 45] Most of the trials did not require adjustment for baseline imbalance as study groups appeared to be comparable. The one exception to this was a trial in which baseline body weight was noted to be higher in orlistat-treated patients ($p<0.05$).[44] Methods used to adjust for this were not described. Eight trials described ways in which missing data were dealt with,[37, 39-44, 47] and nine included analyses based on intention-to-treat.[37, 39-44, 46, 47] All trials reported the numbers of withdrawals per

treatment group with reasons. Patient adherence with the study regimen was assessed in ten trials,[37-43, 45-47] but in four of these this involved the run-in period only.[40, 42, 46, 47]

Quality assessment of RCTs from company submission

Three trials were included from company submissions.[48-50] ***[Details commercial in confidence]***

Results for RCTs of orlistat

The most important findings have been outlined in the text of the review. The reader may also refer to the data extraction tables (appendix 4) for more detailed information, for example to see specific values in connection with study outcomes, where these are not mentioned in the text. 'Significant' means statistically significant unless otherwise stated.

Eleven published trials of orlistat were identified.[37-47] Two trials had a 12 week endpoint,[37, 38] two had a six month endpoint,[39, 45] two had a one-year endpoint,[40, 46] four reported results of a one year weight loss programme followed by a one year weight maintenance programme,[41-43, 47] and one focusing solely on weight maintenance.[44] In addition, three trials were included from company submissions.[48-50]

RCTs with 12 week endpoint

Two RCTs conducted by the same research group were identified.[37, 38] Both trials were small, recruiting numbers per treatment arm of approximately 20,[38] and 45.[37]

In the earlier trial, obese, otherwise healthy patients were recruited, aged 18-55 years, with body weight 20-50% above ideal measurement.[38] The other trial had the following inclusion criteria: obese patients, otherwise healthy, aged 25-60 years, with BMI 27.8-35.0 kg/m^2 for men and 27.3-35.0 kg/m^2 for women.[37] Participants in both trials underwent a four-week, single-blind, placebo run-in period when they were instructed to commence a calorie restricted diet with an energy deficit of 500 kcal/day, which continued during the double-blind treatment phase.[37, 38]

In the earlier trial, participants were only eligible to enter the double-blind phase if they had achieved a weight loss of 0.5-4.0 kg during the run-in period. They were then randomly allocated to receive either orlistat 50 mg three times per day (tid) or placebo for 12 weeks.[38] For the other trial, patients were eligible to enter double-blind treatment if they had adhered to both the dietary and drug regimens. Adherence with the dietary programme was defined as body weight reduction of 0-4 kg (note: this includes no weight loss at all) and a deviation of less than 20% from the prescribed intake of total calories and calories as fat in three out of four calculations from dietary records. Adherence with the drug regimen was assessed by counting returned placebo capsules; at least 80% should have been used. This was a dose-ranging study in which patients were allocated to receive orlistat 120 mg tid, orlistat 60 mg tid, orlistat 10 mg tid, or placebo.[37]

Patients receiving the highest dose of orlistat (120 mg tid) lost significantly more weight compared with placebo (-4.74 kg versus –2.98 kg, p=0.001, values adjusted for weight loss during run-in), however comparisons between other groups did not result in a statistically significant difference.[37] For the other trial, patients in the orlistat group (50 mg tid) lost significantly more weight than those receiving placebo (loss of 4.3 kg versus loss of 2.1 kg, 95% CI for the difference in weight loss 0.2, 4.2). Weight loss was assessed from the start of randomisation.[38]

In terms of cardiovascular risk factors, cholesterol and triglyceride levels did not change during the study in either group, in the earlier trial. In addition, there were no significant changes in blood pressure, heart rate, biochemical or haematological parameters in either group. It is unclear whether these outcomes were assessed from the start of the run-in period, or from the start of randomisation.[38] For the dose-

ranging trial, patients receiving the two higher doses of orlistat achieved significantly reduced levels of total cholesterol and LDL-C. LDL-HDL ratio was significantly reduced in the highest dose orlistat group compared to placebo. There were no statistically significant between-group differences in levels of triglycerides at 12 weeks.[37]

Adverse events and withdrawals

In one trial, one patient withdrew from the orlistat group due to adverse events which included episodes of faecal incontinence. The incidence of adverse events did not differ significantly between groups, with the exception of gastrointestinal adverse events, which were more frequent in the orlistat group. Gastrointestinal effects included abdominal pain, liquid stools, faecal incontinence, urgency, oily stools, nausea, vomiting, flatulence, and haemorrhoids, most of which were reported as mild or moderate in intensity. For most patients, serum levels of vitamins A and E remained within reference values during the trial. Changes in serum levels of vitamin D and beta-carotene were not reported in the paper.[38]

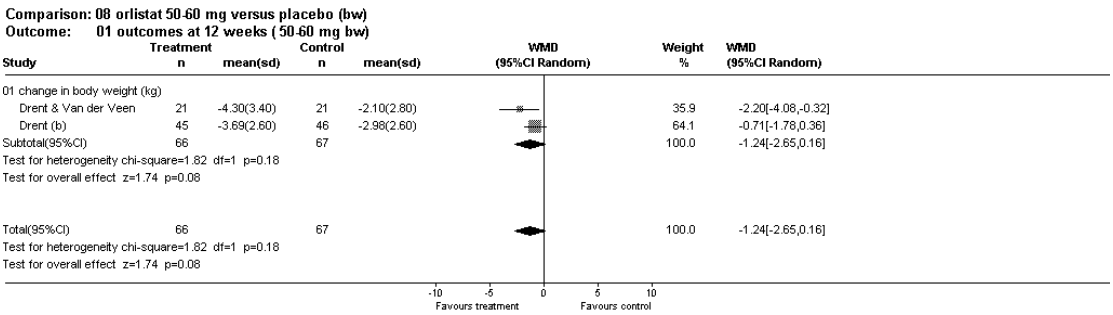
In the dose-ranging trial, there were no statistically significant between-group differences for change in serum levels of vitamins A and D at 12 weeks. However, there were significant reductions in serum levels of vitamin E in the orlistat 60 mg tid and 120 mg tid groups compared with placebo. Most adverse events were reported as mild to moderate. These were described as being common in the orlistat groups, particularly at the two higher doses. Severe adverse events, defined as those that were very inconvenient to patients, were observed in small percentages of patients, again at the two higher doses. One patient in the orlistat 10 mg tid group withdrew due to adverse effects, and four in the 120 mg tid group.[37]

Pooled analyses of RCTs with 12 week endpoint

Results from both trials were pooled for change in body weight at 12 weeks comparing orlistat 50-60 mg tid with placebo.[37, 38] The pooled between-group difference was not statistically significant: WMD –1.24 kg (95% CI: -2.65, 0.16, p=0.08, test of heterogeneity chi-square=1.82, df=1, p=0.18) (figure 1).

Figure 1

Change in body weight at 12 weeks for orlistat 50-60 mg tid versus placebo



RCTs with a six month endpoint

Two trials were identified,[39, 45] one of which was a dose-ranging study.[39]

In one trial, patients aged 18-75 years with a BMI of at least 30 kg/m^2 were included. All patients underwent a two-week, single-blind, placebo run-in period, and commenced a calorie restricted diet (minimum intake 1200 kcal/day) with an energy deficit of 600 kcal/day, to continue during the double-blind phase. During the double-blind phase, patients were randomised to receive orlistat 120 mg tid or placebo. Around 60 participants were allocated per treatment arm.[45]

All reported changes were assessed relative to baseline values. At 24 weeks, the mean weight loss in the orlistat group was –10.75 kg and –7.34 kg for placebo. The results of tests of statistical significance were not reported. There was no statistically significant difference between groups for the number of patients achieving a reduction in BMI of less than 4 kg/m^2, however, more patients in the orlistat group achieved a reduction of between four and 12 kg/m^2 relative to placebo (48% versus 28%, $p<0.05$).[45]

More patients in the orlistat group achieved reduction in total cholesterol levels, LDL-C levels, and LDL-HDL ratio, however the results of tests of statistical significance were not reported. Levels of high-density lipoprotein cholesterol (HDL-C) increased by 0.95% in orlistat patients, and decreased by 2.5% in placebo patients. Total triglycerides decreased by 5.32% and increased by 7.1% respectively. There were no

statistically significant differences between treatment and control groups in mean values of SBP and DBP. Analysis of heart rate, ECG, and laboratory tests showed no significant differences between groups.[45]

Adverse events and withdrawals

One orlistat-treated patient withdrew due to adverse events versus none in the placebo group. Twenty-nine patients in the orlistat group and 11 in the placebo group complained of gastrointestinal adverse events. Of these, 27 and eight patients respectively, suffered from oily stools. The intensity of adverse effects was described as usually mild or moderate.[45]

For the dose-ranging trial, patients aged at least 18 years with a BMI 28-43 kg/m^2 were eligible for inclusion. All patients underwent a four-week, single-blind, placebo run-in period, when a calorie restricted diet was prescribed. The minimum daily intake was 1200 kcal/day and the energy deficit was 600 kcal/day. This continued during the double-blind treatment period when patients were randomised to receive orlistat 240 mg tid, 120 mg tid, 60 mg tid, 30 mg tid, or placebo. Around 120 participants were allocated per treatment arm.[39]

The percentage weight loss relative to initial weight at 24 weeks ranged from 9.3% for the orlistat 240 mg tid group to 6.5% for the placebo group. It was unclear if the weight loss was dose-dependent. Analysis based on least squares mean differences indicated that weight losses in the 60 mg tid, 120 mg tid, and 240 mg tid were all significantly better than placebo ($p \leq 0.002$). The percentage of patients losing more than 10% of their initial body weight ranged from 19% in the placebo group to 38% in the highest orlistat dose group. The respective range of reductions in waist circumference were from 3.5 cm to 6.0 cm.[39]

Adverse events and withdrawals

The rate of withdrawal due to adverse events was 2% in the placebo group, 6% in the orlistat 30 mg tid group, 5% for 60 mg tid, 2% for 120 mg tid, and 3% for 240 mg tid. The rates of adverse events were 69% for placebo, 79% for 30 mg tid, 83% for 60 mg tid, 84% for 120 mg tid, and 87% for 240 mg tid. Most adverse events were described

as mild to moderate in intensity. With the exception of gastrointestinal adverse effects, they were considered to be mostly unrelated to treatment. Rates of gastrointestinal adverse events in the different groups were 46% for placebo, 61% for 30 mg tid, 76% for 60 mg tid, 71% for 120 mg tid, and 83% for 240 mg tid. Most of the orlistat-treated patients experienced one or two episodes of gastrointestinal events, generally within the first few weeks of initiating treatment. Eleven patients withdrew due to gastrointestinal events, 10 of whom were treated with orlistat.[39]

No abnormalities were observed from laboratory tests, ECG measurements, or vital signs, associated with orlistat use. The percentage of patients with low serum levels of fat-soluble vitamins on two or more consecutive occasions ranged between 3.3% for the placebo group, and 12.8% for the highest dose of orlistat, and appeared to be dose-related.[39]

RCTs with a one-year endpoint

Two trials with a one-year endpoint were identified.[40, 46]

One recruited only people with type-2 diabetes maintained on oral sulfonylureas for the six months prior to the trial.[46] Additionally, eligible patients had a stable blood glucose, were aged over 18 years and had a BMI between 28 and 40 kg/m^2. All patients underwent a five-week, single-blind, placebo run-in period. During this time a mildly hypocaloric diet was commenced. Those who achieved at least 70% adherence with the drug regimen during the run-in, assessed by counting returned placebo capsules, were eligible to enter the double-blind trial, when they were randomised to receive either orlistat 120 mg tid or placebo. Around 160 participants were allocated per treatment arm.[46]

Intention-to-treat analysis of the least squares mean difference in weight loss between treatment groups was 2.4 kg in favour of the orlistat group ($p<0.001$), calculated from the beginning of the run-in period to endpoint. Forty-nine percent of patients in the orlistat group and 23% in the placebo group lost at least 5% of their initial weight, and the between group difference was statistically significant ($p<0.001$). The respective figures for at least 10% loss of initial body weight were 18% and 9% ($p<0.02$). The

mean decrease in waist circumference was 4.8 cm for the orlistat group and 2.0 cm for the placebo group ($p<0.01$).[46]

Orlistat patients achieved significantly better glycaemic control compared to placebo patients, in terms of decreased glycosolated haemoglobin (-0.28% versus 0.18%, $p<0.001$) and fasting plasma glucose (-0.02 mmol/l versus 0.54 mmol/l, $p<0.001$). A total of 43% of orlistat-treated patients decreased the dose of sulfonylureas, compared with 29% of the placebo group, and 12% of orlistat-treated patients discontinued sulphonylurea medication compared to none in the placebo group. The between group difference for mean decrease in fasting insulin levels at one year was not statistically significant. In addition, orlistat resulted in significantly greater improvements than placebo in several lipid parameters, including greater reductions in total cholesterol ($p<0.001$), LDL-C ($p<0.001$), triglycerides ($p<0.05$), apolipoprotein B ($p<0.001$), and LDL-HDL cholesterol ratio ($p<0.001$).[46]

Adverse events and withdrawals

Seventy-nine percent of orlistat patients experienced at least one gastrointestinal adverse event compared with 59% of placebo patients. Mild to moderate transient gastrointestinal events were reported with orlistat therapy, usually occurred early during treatment and usually resolved spontaneously. There were 12 withdrawals due to adverse events in the orlistat group and 23 in the placebo group. Withdrawals due to gastrointestinal adverse events totalled seven in the orlistat group and two in the placebo group. Serum levels of fat soluble vitamins generally remained within the reference range, apart from levels of vitamin E and beta-carotene which were significantly lower in the orlistat group versus placebo at one year ($p<0.001$). Vitamin D supplementation was required in 17% of orlistat patients and 7% of control patients, vitamin E in 1% of both groups, and beta-carotene in 9% of the orlistat group. Prothrombin times did not differ between groups and did not fall below the reference range.[46]

In the second trial, participants with a minimum age of 18 years and BMI 30-43 kg/m^2 were recruited. Patients with diabetes were excluded. All participants underwent a four-week, single-blind, run-in, during which time they received placebo and commenced a low energy diet. Each individual patient's diet was calculated from

estimated total daily energy expenditure minus 600 kcal/day, with a minimum prescribed energy intake of 1200 kcal/day. This dietary regimen continued for the first 24 weeks of the double-blind phase. After this the prescribed daily energy intake was further reduced by 300 kcal/day for all patients regardless of whether or not body weight had stabilised. Those initially prescribed the minimum energy intake (1200 kcal/day) had energy intake adjusted to 1000 kcal/day at the end of week 24 and maintained to the end of week 52. Patients were randomised to receive orlistat 120 mg tid or placebo for one year. One hundred and fourteen participants were allocated to each treatment group.[40]

The between group difference for average percentage weight loss at 52 weeks, analysed by intention-to-treat, was statistically significant at 8.5% in the orlistat group and 5.4% in the placebo group ($p=0.016$). It was not clear if the change in body weight was assessed from the beginning of the run-in period or randomisation. The least squares mean difference from placebo for change in body weight was 2.0 kg (95% CI: -3.6, -0.38, $p<0.05$) for orlistat-treated patients based on intention-to-treat. The between group differences for patients losing more than 5% and 10% initial body weight during double-blind treatment were statistically significant in favour of orlistat. The respective values were 35% versus 21% ($p=0.02$) and 16% versus 6% ($p=0.02$). The between-group difference for mean decrease in waist circumference at one year was not statistically significant.[40]

Changes in lipid levels were assessed from the beginning of randomisation. Orlistat treated patients showed statistically significant decreases in serum levels of total cholesterol, LDL-C, and LDL-HDL ratio compared with placebo ($p<0.05$). However, there were no statistically significant between-group differences for triglycerides, lipoprotein (a), and very-low-density lipoprotein cholesterol (VLDL-C). Levels of HDL-C increased by similar amounts in both groups. In patients with an elevated level of LDL-C at baseline (≥3.36 mmol/l), the mean value decreased after one year by 7.1% in the orlistat group and by 1.3% in the placebo group. There was a trend towards a reduction in fasting insulin, and, to a lesser extent, in fasting glucose levels associated with weight loss in both groups.[40]

Adverse events and withdrawals

Nine (8%) patients in the orlistat group withdrew due to adverse events compared with seven (6%) in the placebo group. Eighty-two percent of patients in the orlistat group and 56% in the control group reported at least one gastrointestinal adverse event. Most events occurred early in the study and were transient (≤4 days). Three orlistat-treated patients and one placebo-treated patient withdrew due to gastrointestinal adverse events. Supplementation of vitamins A, D, and E was given to 1.8%, 8.0%, and 3.6% respectively of orlistat-treated patients, compared with 0.9% of placebo patients for each vitamin. During the study, 7% of orlistat patients and 11% of placebo patients developed gallbladder abnormalities, and 3% and 2% respectively developed renal abnormalities.[40]

RCTs of weight loss / weight maintenance

Four RCTs reported results of a one year weight loss programme followed by a one year weight maintenance programme.[41-43, 47]

In the first trial, participants aged over 18 years with a BMI of 30-43 kg/m^2 were recruited. People with type-2 diabetes treated with drugs were excluded. All patients underwent a four-week, single-blind, placebo run-in period, when they were instructed to commence an energy restricted diet. Those with a treatment adherence of at least 75%, assessed by counting returned placebo capsules, were randomised to receive orlistat 120 mg tid or placebo for one year, as a weight loss regimen. Patients completing the first year of treatment, with a treatment adherence of least 70%, were eligible to enter the maintenance phase. Participants treated with orlistat during year one were randomised to receive placebo, orlistat 60 mg tid, or orlistat 120 mg tid. Participants taking placebo during year one continued to take placebo during year two. This was a large trial, with 657 participants allocated to the initial orlistat group and 224 to the placebo group.[41]

Changes in outcomes appeared to be reported from the beginning of randomisation. At the end of year one, orlistat-treated patients lost significantly more weight than placebo (8.76 kg versus 5.81 kg, $p<0.001$). There were statistically significant results in favour of orlistat for those losing at least 5% and 10% of initial weight. The values

were 66% versus 44% ($p<0.01$) and 39% versus 25% ($p<0.004$) respectively. In addition, there were small but statistically significant improvements in the orlistat group versus placebo for mean decreases in DBP ($p=0.009$) and SBP ($p=0.002$) at one year.[41]

In terms of weight regain at the end of year two, the mean values were 3.2 kg for the orlistat 120 mg tid group, 4.3 kg for the orlistat 60 mg tid group, and 5.6 kg for the placebo group ($p<0.001$ for placebo versus 120 mg, and for 60 mg versus 120 mg). The mean percentage weight loss at two years was 7.6% for 120 mg, 4.2% for 60 mg and 4.5% for placebo. Tests of statistical significance were not reported for these comparisons. Those maintaining greater than 10% initial loss at 2 years was 34% in those receiving orlistat 120 mg tid for two years, and 18% in those receiving placebo for two years ($p=0.02$).[41]

Results for changes in lipid levels and indicators of glycaemic control were presented for those receiving orlistat 120 mg tid for two years and those receiving placebo for two years. Orlistat-treated patients had significantly lower levels of total cholesterol, LDL-C, HDL-C, and triglycerides. Results from ANCOVA suggested that the changes in lipid levels were independent of weight loss. More favourable results were also observed for orlistat for changes in fasting serum glucose and insulin levels over two years ($p=0.001$ and $p=0.04$ for the respective between group differences between orlistat and placebo). The observed decrease in insulin levels appeared to be related to weight loss, rather than being an independent drug effect.[41]

Adverse events and withdrawals

During year one, 61 patients (9%) in the orlistat group withdrew because of adverse effects compared with nine patients (4%) in the placebo group. The figures at the end of year two were 5 (3.3%) for those receiving orlistat 120 mg tid for the full two years, 9 (6%) for those receiving orlistat 120 mg tid during year one and 60 mg tid during year two, 6 (4%) for those receiving orlistat in year one and placebo in year two, and 4 (3%) for patients receiving placebo for two years. At the end of year two 79% of patients receiving orlistat 120 mg tid for the full two years reported at least one gastrointestinal adverse event compared with 59% for those receiving placebo for two years. The respective numbers of withdrawals due to gastrointestinal adverse events were seven patients and two patients respectively at the end of two year. The authors stated that most gastrointestinal adverse events occurred early during treatment, were mild to moderate in intensity, and resolved spontaneously. The adverse event rate was lower in year two than in year one and not differ significantly between groups. There were no apparent systematic differences in weight loss among participants who experienced several, one, or no gastrointestinal adverse events. At the end of year two, 14% of patients receiving 120 mg tid for two years and 7% of patients receiving placebo for two years required supplemental fat-soluble vitamins or beta-carotene. Although serum levels of vitamins D and E decreased significantly in those receiving orlistat, values remained within the reference ranges.[41]

The incidence of breast cancer was assessed during this trial. Among those receiving orlistat 120 mg tid for two years, there were three cases of breast cancer diagnosed, two identified prior to starting the trial, and one identified 32 days after randomisation. Among those receiving placebo for two years, there was one case of breast cancer identified prior to the start of the trial.[41]

In the second trial, participants aged over 18 years, with BMI between 30 and 44 kg/m^2 were recruited. All eligible patients entered a four-week, single-blind, placebo run-in period, when they commenced a reduced energy diet with a prescribed intake of 1200 kcal/day for patients weighing less than 90 kg initially and 1500 kcal/day for those weighing 90 kg or more initially. Patients with at least 75% adherence with drug regimen during the run-in period, assessed by counting returned placebo

capsules, were eligible to enter the double-blind trial. The above dietary regimen continued throughout the first year of the trial, and, in addition, patients viewed videos on behaviour modification. Patients were randomised to receive orlistat 120 mg tid, orlistat 60 mg tid, or placebo. Around 210 participants were allocated to each treatment group. Year two constituted the weight maintenance phase, and the drug regimens continued as above. A weight maintenance diet was prescribed for those who were still losing weight and patients were encouraged to walk briskly for 20-30 minutes three to five times per week.[42]

Changes in outcomes were calculated from randomisation. At the end of year one, intention-to-treat analysis showed that both orlistat groups had achieved a significantly greater decrease in weight relative to placebo ($p=0.001$). The mean weight loss in the orlistat 120 mg tid group was 7.94 kg compared with 7.08 kg for the 60 mg tid group and 4.14 kg in the placebo group. A similar pattern was seen for proportions of patients losing at least 5% and 10% of their initial weight, with both active treatment groups performing significantly better than placebo for both outcomes ($p<0.001$). The values were 51% for the orlistat 120 mg tid group, 49% for the 60 mg group, and 31% for the placebo group for at least 5% weight loss, and 29%, 24%, and 11% respectively, for at least 10% weight loss.[42]

At the end of year two, intention-to-treat analysis showed that both orlistat groups had achieved a significantly greater decrease in weight relative to placebo ($p=0.001$). The mean weight loss in the orlistat 120 mg tid group was 5.02 kg compared with 4.46 kg for the 60 mg tid group and 1.65 kg in the placebo group. The percentage of initial body weight lost at two years was 5.01% for 120 mg group, 4.44% for 60 mg group, and 1.70% for the placebo group ($p<0.001$ for both orlistat groups compared with placebo). Weight regain at year two, expressed as a percentage of the weight lost during year one was 38% for the 120 mg group, 37% for the 60 mg group, and 60% for the placebo group.[42]

At two years, both active treatment groups performed significantly better than placebo in terms of maintaining a weight loss of at least 5% of initial body weight. The values were 34% for both orlistat groups, and 24% for the placebo group ($p<0.03$ for 60 mg tid versus placebo and $p<0.02$ for 120 mg tid versus placebo). A similar pattern was

seen for proportions of patients maintaining a weight loss of at least 10% of initial body weight. The values were 19% for the orlistat 120 mg tid group, 15% for the orlistat 60 mg tid group, and 7% for the placebo group (p=0.008 for 60 mg tid versus placebo and p<0.001 for 120 mg tid versus placebo).[42]

At the end of year one, total cholesterol and LDL-C levels were significantly lower in both of the orlistat groups compared with placebo (p=0.001), and this was generally maintained during year two. Between-group differences for triglycerides and glucose levels were never statistically significant. Fasting insulin levels in the orlistat 120 mg tid group were lower than placebo at one year (p<0.05). DBP decreased in the orlistat 60 mg tid group at one year (-0.97±0.01 mm Hg; p=0.02); changes in the other two groups were not statistically significant. During year two no significant changes were observed between groups for DBP, but SBP in the orlistat 120 mg tid group was reduced relative to placebo (p=0.04). Similar results were seen for intention-to-treat and completer analyses.[42]

Adverse events and withdrawals

Withdrawals due to adverse events over the two years were 11% in the 120 mg tid group, and 7% in both the other groups, and rates did not differ significantly between groups. Patients reporting gastrointestinal adverse events over the two years were 79% in the orlistat 120 tid group, 72% in the 60 mg tid group, and 59% for placebo (p=0.003 60 mg tid versus placebo, p=0.001 120 mg tid versus placebo). Gastrointestinal adverse events occurred more frequently in the orlistat groups versus placebo (p=0.001). Most gastrointestinal events were described as mild to moderate in intensity, were limited to one or two episodes per patient, and occurred early during treatment. Few gastrointestinal adverse events were reported during year two. Withdrawal due to gastrointestinal adverse events were 5.7% in the 120 mg group, 4.7% in the 60 mg group, and 1.4% for placebo.[42]

Serum levels of vitamins A, D and E and beta-carotene remained within reference ranges in all groups throughout the two years. Two consecutive low vitamin E and beta-carotene values occurred significantly more frequently in patients treated with orlistat than with placebo. The frequency of two consecutive low level vitamin A and

D values did not significantly differ between groups. Beta-carotene supplementation was required by 6.3% in the orlistat 120 mg tid group, 4.3% in the orlistat 60 mg tid group, and 2.4% in the placebo group.[42]

For the third trial, obese patients were recruited from hospital waiting lists or by local advertising. Patients aged at least 18 years, with a BMI between 28-47 kg/m^2 were eligible to enter the trial. Those with pharmacologically treated diabetes were excluded. All patients underwent a four-week, single-blind, placebo run-in period, and they commenced an energy restricted diet. The energy content of the diet was calculated from each patient's estimated total daily energy expenditure minus 600 kcal/day. The minimum prescribed energy intake was 1200 kcal/day. Participants with more than 75% adherence during the run-in regimen, assessed by counting the number of returned placebo capsules, were eligible to enter the double-blind phase. For the weight loss phase, the above dietary regimen was followed until week 24, then the prescribed energy intake was further reduced by 300 kcal/day, and the minimum prescribed energy intake was adjusted to 1000 kcal/day. Patients were randomised to receive orlistat 120 mg tid or placebo. At this stage, 340 participants were allocated per treatment arm. After one year, patients could enter the weight maintenance phase provided they demonstrated more than 75% adherence with the weight loss regimen, assessed as above. During year two, a weight maintenance diet was commenced, and patients were advised not to follow a hypocaloric diet during this time. They were re-randomised to either orlistat 120 mg tid or placebo.[43]

The least squares mean difference in weight loss during year one was 3.9 kg in favour of orlistat ($p<0.001$), calculated from the beginning of the run-in period to the end of year one. Patients losing 0.1-5.0% initial body weight at the end of year one were 24% for orlistat and 33% for placebo. The figures for those losing 5.1-10.0% of initial weight were 30% and 32% respectively; 30% and 16% for loss of 10.1-20.0% of initial weight; and 9% and 2% for loss of more than 20% initial body weight. Patients with unchanged or increased body weight at the end of year one were 8% and 18% respectively.[43]

During year two, for the group receiving placebo during year one and orlistat during year two, the least squares mean difference in weight loss versus the group receiving

orlistat during year one and placebo during year two was 3.6 kg, in favour of the former ($p<0.001$). For the group receiving orlistat during both years, the least squares mean difference in weight loss versus the group receiving placebo during both years was 2.4 kg in favour of orlistat ($p<0.001$). At two years, 57% of patients receiving orlistat for two years maintained a weight loss greater than 5%, versus 37% in those receiving placebo for two years.[43]

The group receiving orlistat during the first year and the group receiving orlistat for two years had significantly greater reductions in total cholesterol, LDL-C, LDL-HDL ratio, glucose, and insulin, when compared with the groups receiving placebo for one and two years respectively. There were significantly greater reductions in SBP and DBP at one year in the orlistat group versus placebo. Linear modelling showed that baseline risk-factor value and weight reduction were significant variables at one and two years for observed risk-factor changes. Treatment was also a significant predictor for change in total cholesterol at 1 year ($p=0.0001$) and at 2 years ($p=0.0002$), and for change in LDL-C at 1 year ($p=0.0003$) and at 2 years ($p=0.0463$). At two years, treatment was also a significant predictor ($p=0.0236$) for change in LDL-HDL ratio.[43]

Adverse events and withdrawals

During year one, 12/345 (3.5%) patients reported gastrointestinal adverse effects in the orlistat group versus 2/343 (0.6%) patients in the placebo group. During year two, the figures were 2/126 (1.6%) patients in those receiving placebo over two years, zero for those receiving orlistat then placebo, 5/127 (3.9%) for those receiving placebo then orlistat, and 2/135 (1.5%) for those taking orlistat for two years. There were no clinically or statistically significant changes in the mean values of any laboratory measurements during the study, and the frequency of laboratory abnormalities was evenly distributed between groups.[43]

During year one, 41 patients in the orlistat group and 18 in the placebo group had two or more consecutive low serum levels of fat soluble vitamins but only 16 and four patients respectively required supplements. During year two, supplemental vitamins were received by four patients in the orlistat/orlistat group, one in placebo/placebo group, three in the placebo/orlistat group, and one in the orlistat/placebo group.[43]

In the fourth trial, patients aged at least 18 years, with a BMI between 28-43 kg/m^2, were recruited. People with drug-treated diabetes mellitus were excluded. All patients entered a four-week, single-blind, placebo run-in period when they were instructed to commence a dietary regimen containing 30% of calories as fat, with a daily energy deficit of 600 kcal. Patients who completed the run-in period and achieved at least 75% adherence with the treatment regimen (assessed by counting returned placebo capsules) were eligible to enter the double-blind study. For all patients, the diet described above continued throughout year one. During year two, dietary intake was adjusted to achieve weight maintenance rather than weight loss. Patients were randomised to receive orlistat 120 tid, orlistat 60 mg tid, or placebo, all for two years, with approximately 240 participants allocated per treatment arm.[47]

The following data are based on intention-to-treat analyses. From the beginning of the run-in period to the end of year one, the mean weight change was –9.4 kg in the orlistat 120 mg tid group, -8.5 kg in the orlistat 60 tid mg group, and –6.4 kg in the placebo group ($p<0.001$ for both orlistat groups versus placebo). The mean weight change from start of run-in to the end of two years was –7.4 kg in the orlistat 120 mg tid group, -6.6 kg in the orlistat 60 mg tid group, and –4.3 kg in the placebo group ($p<0.005$ for orlistat 60 mg tid versus placebo and $p<0.001$ for orlistat 120 mg tid versus placebo). Proportions of patients achieving greater than 10% loss of initial body weight at one year was 38% in the orlistat 120 mg tid group, 31% in the orlistat 60 mg tid group, and 19% in the placebo group ($p<0.002$ for orlistat 60 mg tid versus placebo and $p<0.001$ for orlistat 120 mg tid versus placebo). At the end of two years 28% of patients in the orlistat 120 mg tid group had maintained more than 10% loss of initial weight compared with 29% in the 60 mg tid group and 19% in the placebo group ($p<0.05$ for both orlistat groups versus placebo). There were no statistically significant differences between groups for mean change in waist circumference at one year. However, at the end of two years, the values were –5.1 in the orlistat 120 mg tid group, -4.7 in the 60 mg tid group, and –3.1 in the placebo group ($p<0.05$ for orlistat 120 mg versus placebo).[47]

In terms of changes in lipid levels, both orlistat groups achieved statistically significant improvements in total cholesterol and LDL-C at one and two years compared with placebo ($p<0.001$). Increased levels of HDL-C were seen in all groups

at years one and two, but the between-group difference was statistically significant only for orlistat 120 mg tid versus placebo at one year ($p<0.05$). Greater improvements in the LDL-HDL ratio were seen in orlistat groups relative to placebo at years one and two ($p<0.001$ for orlistat 60 mg tid versus placebo at years one and two and orlistat 120 mg tid versus placebo at year two; $p<0.05$ for orlistat 120 mg tid versus placebo at year one). No statistically significant differences between groups were seen for triglyceride or VLDL-C levels at either time point.[47]

DBP was significantly lower in orlistat 120 mg tid patients compared with placebo patients at one year ($p<0.05$). No statistically significant between-group differences were observed for measurements of SBP. Orlistat-treated patients appeared to achieve a better quality of life at one and two years. This outcome was assessed using a 55-item self-administered questionnaire.[53]

Adverse events and withdrawals

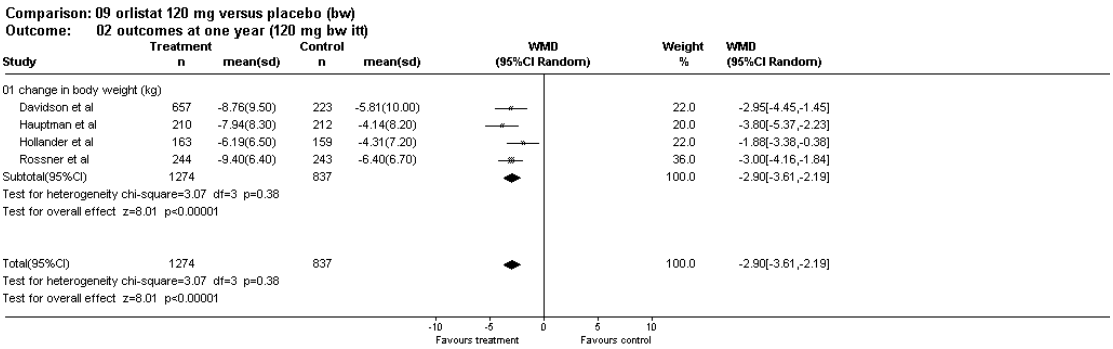
During year one 26% of patients withdrew from the orlistat 120 mg tid group, 24% from the 60 mg tid group, and 35% from the placebo group. Of these 6%, 7%, and 2% respectively withdrew due to adverse events, and 3%, 2%, and 2% withdrew due to treatment failure. During year two, the figures for withdrawal were orlistat 120 mg tid group 12%, 60 mg tid group 24%, and placebo 14%. Of these 9%, 10%, and 3% respectively withdrew due to adverse events, and 3%, 2%, and 3% withdrew due to treatment failure. Gastrointestinal adverse events occurred more frequently in the orlistat groups, and caused 9 patients in the orlistat 120 mg tid group, 12 patients in the 60 mg tid group, and 2 patients in the placebo group, to withdraw.[47]

Pooled analyses of RCTs with one- and two-year endpoints

Four trials were pooled that had analysed by intention-to-treat at one year.[41, 42, 46, 47] The summary estimate showed that orlistat 120 mg tid achieved statistically significant greater weight loss compared with placebo: WMD –2.90 kg (95% CI: -3.61, -2.19, $p<0.00001$, chi-square test for heterogeneity 3.07, df=3, $p=0.38$) (figure 2).

Figure 2

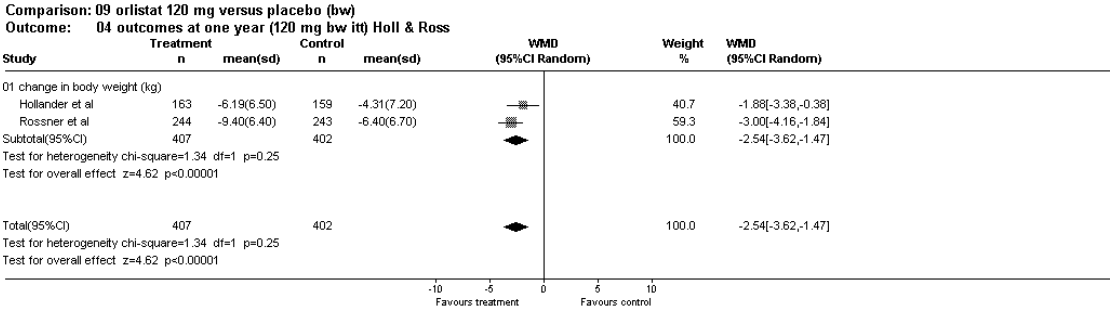
Weight change at one year for orlistat 120 mg tid versus placebo



It should be noted that two of these trials calculated outcomes from the start of the run-in period,[46, 47] whilst the other two calculated outcomes from the start of double-blind treatment.[41, 42] The analysis was repeated grouping trials according to the starting point of calculations. For the two trials calculating change in body weight from the start of the run-in period, the summary effect size was slightly smaller compared with the previous analysis: WMD –2.54 kg (95% CI: -3.62, -1.47, p<0.00001, chi-square test for heterogeneity 1.34, df=1, p=0.25) (figure 3).[46, 47]

Figure 3

Change in body weight at one year for orlistat 120 mg tid versus placebo

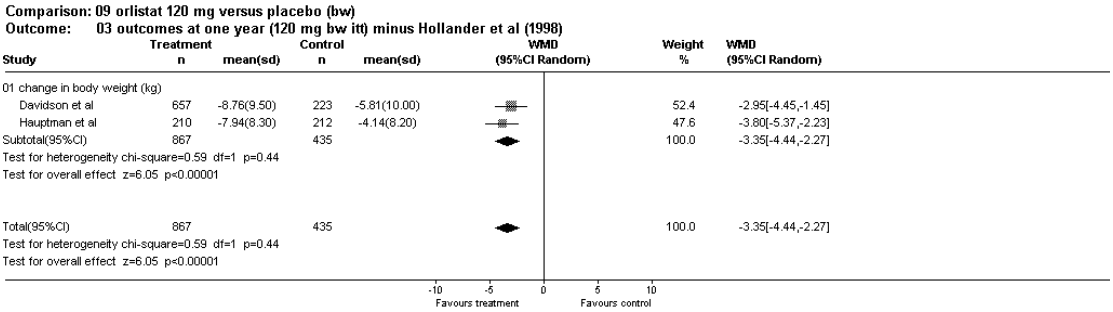


For the two trials calculating change in body weight from the start of the double-blind period, the summary effect size was slightly larger compared with the original

analysis: WMD –3.35 kg (95% CI: -4.44, -2.27, p<0.00001, chi-square test for heterogeneity 0.59, df=1, p=0.44) (figure 4).[41, 42]

Figure 4

Change in body weight at one year for orlistat 120 mg tid versus placebo

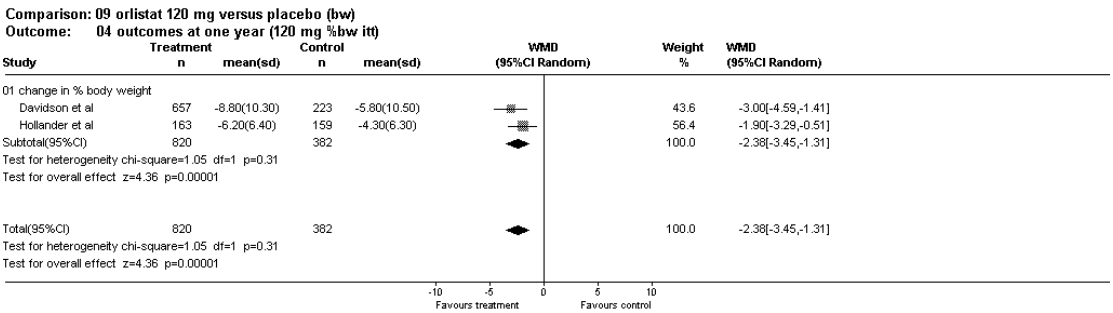


Two trials were not included in these meta-analyses.[40, 43] This is because insufficient data were provided in the papers to calculate effect sizes.

Two trials were pooled for change in percentage body weight at one year.[41, 46] WMD –2.38% (95% CI: -3.45, -1.31, p<0.00001, chi-square test for heterogeneity 1.05, df=1, p=0.31) (figure 5). It should be noted that one of these trials calculated the outcome from the start of the run-in period,[46] and the other calculated the outcome from the start of double-blind treatment.[41] Four trials were excluded from this meta-analysis: two due to lack of variance data,[40, 43] and two because the outcome was not reported.[42, 47]

Figure 5

Change in percentage body weight at one year for orlistat 120 mg tid versus placebo

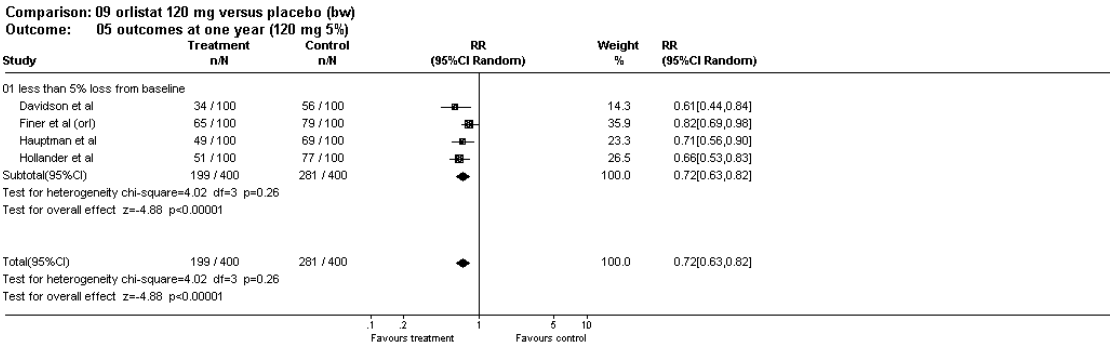


Four trials were pooled for those achieving less than 5% loss of initial weight at one year, and showed that orlistat 120 mg tid performed better than placebo:[40-42, 46] RR 0.72 (95% CI: 0.63, 0.82, p<0.00001, chi-square test for heterogeneity 4.02, df=3, p=0.26) (figure 6).

In three trials it was not clear whether the outcome had been calculated from the start of the run-in period, or the start of double-blind treatment.[41, 42, 46] In the other trial, it was calculated from the start of double-blind treatment.[40] In three trials analysis appeared to be by intention-to-treat,[40-42] and in the other this was not clear.[46]

It should be noted that one trial was not included in this analysis as the relevant figures were read from a graph, and therefore may not have been accurate.[47] The outcome was not reported in another trial.[43]

Figure 6
Relative risk of failure to achieve at least 5% loss of initial weight at one year for orlistat 120 mg tid versus placebo

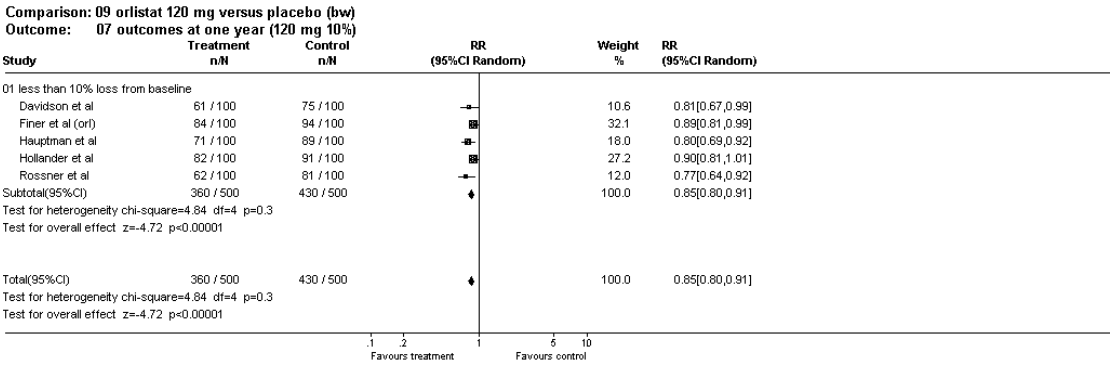


Five trials were pooled for the risk of achieving less than least 10% of initial body weight at one year, and also showed that orlistat 120 mg tid performed more favourably than placebo.[40-42, 46, 47] RR 0.85 (95% CI: 0.80, 0.91, p<0.00001, chi-square test for heterogeneity 4.84, df = 4, p=0.3) (figure 7).

In four trials the starting point used for calculation of the outcome was unclear (i.e. whether at start of run-in or double-blind treatment).[41, 42, 46, 47] In the fifth trial, calculations were from the start of double-blind treatment.[40] In three trials, intention-to-treat analysis was undertaken,[40-42] and in two it was not clear whether this had been done.[46, 47] One trial was excluded from the analysis as results were not reported in terms of achieving at least 10% loss of initial weight.[43]

Figure 7

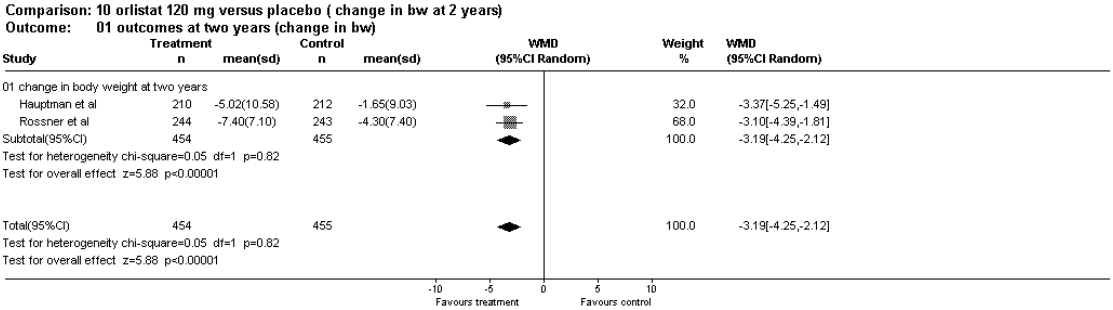
Relative risk of failure to achieve at least 10% loss of initial weight at one year for orlistat 120 mg tid versus placebo



Two trials were pooled for change in body weight at two years, orlistat 120 mg tid versus placebo.[42, 47] The pooled result was in favour of orlistat: WMD –3.19 kg (95% CI: -4.25, -2.12, p=0.00001, chi-square test for heterogeneity 0.05, df=1, p=0.82) (figure 8).

Figure 8

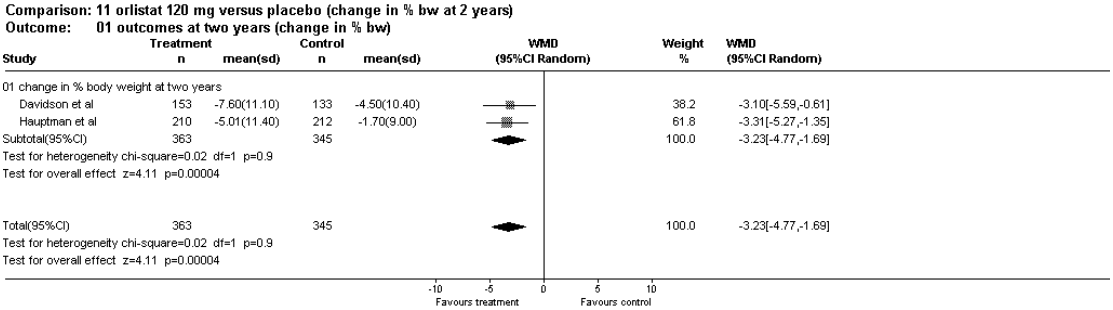
Change in body weight at two years for orlistat 120 mg tid versus placebo



Two trials were pooled for change in percentage body weight at two years, orlistat 120 mg tid versus placebo.[41, 42] The pooled result was in favour of orlistat: WMD –3.23 kg (95% CI: -4.77, -1.69, p=0.00004, chi-square test for heterogeneity 0.02, df=1, p=0.9) (figure 9).

Figure 9

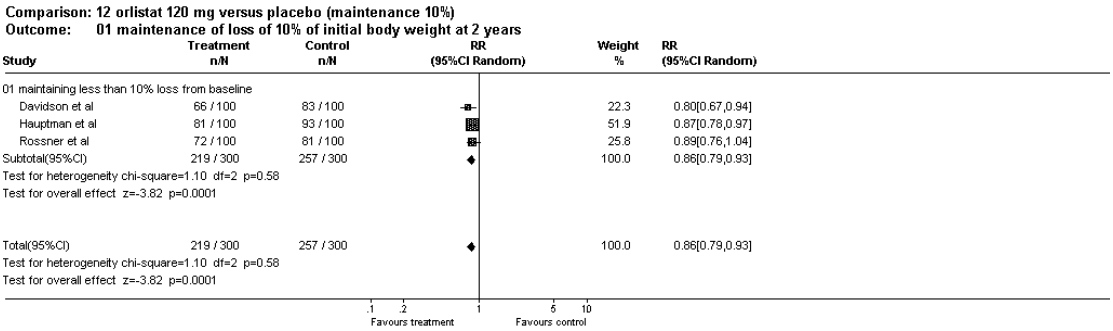
Change in percentage body weight at two years for orlistat 120 mg tid versus placebo



Three trials were pooled for the risk of failing to maintain 10% loss of initial body weight at two years, orlistat 120 mg tid versus placebo.[41, 42, 47] Again, the pooled result was significantly in favour of orlistat: RR 0.86 (95% CI: 0.79, 0.93, p=0.0001, chi-square test for heterogeneity 1.10, df=2, p=0.58) (figure 10).

Figure 10

Relative risk of failure to maintain 10% loss of initial body weight at two years, orlistat 120 mg tid versus placebo



RCTs focusing on weight maintenance

One RCT was identified which was a dose-ranging study for weight maintenance.[44]

Participants aged at least 18 years, with BMI between 28-43 kg/m^2 were recruited, with exclusion of those with type-2 diabetes. All patients underwent a six month run-in period for weight loss. During this time, an energy reduced diet was prescribed, designed to produce weight loss at the rate of 0.5-1.0 kg per week. All participants received dietary counselling, attended four sessions on behavioural modification, and were encouraged to walk briskly for 20-30 minutes five times per week. Patients losing at least 8% of their initial body weight during the run-in were eligible to enter the double-blind phase of the trial, designed to achieve weight maintenance. At this time, each individual's energy requirements were reassessed and an increase in energy intake was prescribed to match anticipated metabolic requirements over the ensuing year. Dietary and behavioural counselling were provided. If patients regained weight, a reduced energy diet was not initiated, but they were encouraged to maintain the higher body weight. Patients were randomised to receive orlistat 120 mg tid, orlistat 60 mg tid, orlistat 30 mg tid, or placebo tid, for one year. Around 180 participants were allocated per treatment arm.[44]

The mean overall weight loss during the six month run-in period was approximately 10 kg. The mean weight loss after one year of double-blind treatment relative to body weight at the start of the run-in period was 7.24 kg for the orlistat 120 mg tid group, 6.16 kg for the orlistat 60 mg tid group, 5.15 kg for the orlistat 30 mg tid group, and 5.93 kg for the placebo group. The between-group difference was statistically significant only for 120 mg tid vs placebo ($p<0.001$). Analysis of weight regain during double-blind treatment, expressed as a percentage of the weight lost during the run-in period, was 32.4% for orlistat 120 mg tid, 47.2% for orlistat 60 mg tid, 53.3% for orlistat 30 mg tid, and 56.0% for placebo ($p<0.001$ for 120 mg dose versus placebo).[44]

Twenty-four percent of patients receiving orlistat 120 mg tid did not regain any weight or continued to lose weight after randomisation compared with 16.3% in the placebo group. After one year of double-blind treatment, body weight was greater than initial body weight in 5.4% of patients in the 120 mg dose group versus 18.3% in the placebo group. Sixty-two percent in the orlistat 120 mg tid group sustained a weight loss of greater than 5% of initial weight compared with 50% of placebo patients.[44]

Reductions in total and LDL-C levels from initial values were significantly greater in all orlistat groups when compared with placebo. Total and LDL-C levels increased in the placebo group. Changes in the LDL-HDL ratio were significantly different only for the 30 mg dose group versus placebo. For fasting glucose and insulin levels, mean increases of 1-2% above initial values were noted in the 30 mg dose and placebo groups compared with slight reductions (around 1%) in the other two orlistat groups. Changes in blood pressure and waist circumference did not differ significantly between groups.[44]

Adverse events and withdrawals

There were 27 withdrawals due to adverse events in the 120 mg dose group, 17 each in the 60 mg and 30 mg groups, and five in the placebo groups. The percentage of patients reporting at least one adverse events was around 7-8% greater in the orlistat groups compared with placebo. This difference was mainly accounted for by more gastrointestinal adverse events in the orlistat groups, with similar rates for adverse

events involving other body systems across groups. The percentage of patients reporting gastrointestinal events was 95% in the 120 mg group, 92% in the 60 mg group, 82% in the 30 mg group, and 68% in the placebo group. Most gastrointestinal adverse events were reported as mild to moderate in intensity, occurred early during treatment, and resolved without intervention. Most patients experienced one or two episodes. The rates of withdrawal due to gastrointestinal adverse events were 12% in the 120 mg group, 7% in the 60 mg group, 5% in the 30 mg group, and less than 1% in the placebo group. The mean serum levels of vitamins A, D, and E, and beta-carotene remained within the reference ranges. However, vitamin E and beta-carotene levels were significantly lower in the orlistat groups compared with placebo at the end of the study ($p<0.001$).[44]

The following section summarises data from company submissions

A brief description of results is presented here. It is important that readers also refer to data extraction tables (appendix 4a) and quality assessment tables (appendix 5a) for detailed information on the trials.

A further three trials on orlistat, submitted by the drug company, were included.[48-50] All three had an endpoint of one year.

In the first trial, patients aged 18-75 years with a BMI between 28 and 38 kg/m^2 were recruited. In addition, eligible patients had to have at least one of the following risk factors: fasting blood glucose of at least 6.7 mmol/l on at least two occasions, or diagnosed with type-2 diabetes; total plasma cholesterol greater than 6.5 mmol/l or plasma LDL-C at least 4.2 mmol/l on at least two occasions, or receiving lipid lowering drugs; DBP greater than 90 mmHg on at least two occasions or receiving antihypertensive treatment. All patients underwent a two-week, single-blind, placebo run-in period when they commenced a hypocaloric diet containing 30% of calories as fat, with an energy deficit of 600 kcal/day. This dietary regimen continued throughout the double-blind treatment phase and additionally patients received dietary counselling and weight control self-help information, and were encouraged to walk for 30 minutes every day. After six months of therapy, patients could opt to reduce energy intake by a further 300 kcal/day. Patients were randomised to receive either orlistat 120 mg tid (n=190) or placebo (n=186).[48]

[Results commercial in confidence]

Adverse events and withdrawals

[Commercial in confidence]

In the second trial, patients aged 18-80 were recruited, with a BMI of at least 28 kg/m^2. In addition, eligible patients had to have at least one risk factor relating to raised lipid levels, impaired glycaemic control, or raised blood pressure (please refer to data extraction table for more details). A mildly hypocaloric diet was prescribed for all patients, and they were randomised to receive either orlistat 120 mg tid (n=265) or placebo (n=266) for one year.[49]

[Results commercial in confidence]

Adverse events and withdrawals

[Commercial in confidence]

In the third trial, obese patients with hypertension were recruited. All patients were prescribed a hypocaloric diet with an energy deficit of 600 kcal per day, and were prescribed a multivitamin supplement. Lifestyle intervention literature was made available, there were periodic meetings with a dietician, and moderate exercise was encouraged. Patients were randomised to receive either orlistat 120 mg tid (n=278) or placebo (n=276), for one year.[50]

[Results commercial in confidence]

Adverse events and withdrawals

[Commercial in confidence]

Economic evaluations

Please refer to appendix 6 for data extraction tables and appendix 7 for quality assessment.

One published report described a cost-utility analysis of orlistat in the treatment of obesity.[51] Data from three double-blind RCTs were used to assess the effectiveness of orlistat.[41, 43, 46] The interventions included orlistat 120 mg tid plus a hypocaloric diet versus placebo with diet. All trials started with a four or five-week run-in period of placebo plus diet, and had a one or two year follow-up. The main outcomes were mean weight loss and the proportion of patients who lost more than 5% of initial body weight.

The prevalence of obesity and the associated morbidity and mortality figures were derived from literature reviews as well as quality of life (QoL) gains due to weight loss and cost data. The perspective adopted was that of the NHS, therefore only direct costs (outpatient appointments, GP consultations, and drugs) were included. Health benefits were quantified in terms of changes in QoL associated with weight loss.

The results were as follows:

- The one-year average cost of orlistat treatment for 100 patients (treated for 2 years) was £73,436
- Orlistat results in obese people losing an additional 3-4% of initial body weight over diet alone. For both orlistat and placebo there was a rebound effect (weight regain) during year 2. The additional one-year weight loss over placebo for type 2 diabetes patients was 1.9%.
- The proportion of patients achieving at least 5% loss of initial body weight over two years, based on an intention to treat analysis, was 17.5% (95% CI: 7.4%, 27.3%) greater for orlistat than for placebo; and the number needed to treat was 6 (95% CI: 4, 14).
- The number of quality adjusted life years (QALYs) gained in a year of 100 patients treated with orlistat, compared to placebo, was estimated at: 1.601.
- The incremental cost utility of orlistat treatment was £45,881 (range: £19,452 to £55,391) per QALY gained.

Sensitivity analyses were performed for the costs of orlistat, different withdrawal rates, different response rates (completers who lost 5% of initial body weight or more) and different utility gains. The analysis seems reasonably stable to these sensitivity analyses.

The authors commented that utilities have been calculated on the basis of the published trial results. However trial data were not consistent with European Agency for the Evaluation of Medicinal Products (EMEA) prescription indication for orlistat (loss of ≥ 2.5 kg by diet in four weeks pre-treatment and loss of ≥ 5% body weight after 12 weeks orlistat treatment). Therefore the cost/QALY gained figures obtained here may be different from those obtained in clinical practice.

Economic evaluations from company submissions

Please refer to appendix 6a for data extraction tables and appendix 7a for quality assessment.

One report was identified which described a cost-utility analysis of orlistat in the treatment of obesity.[52] Clinical effectiveness data were derived from the re-analysis of a published RCT.[43] The interventions included orlistat 120 mg tid plus a hypocaloric diet versus placebo with diet. The trial started with a four-week run-in period of placebo plus diet. The main outcomes were mean weight loss and the proportion of patients who lost more than 5% of initial body weight.

The model included 4 steps:

[Details commercial in confidence; only headline results given]

The **…**synthesis of costs and benefits resulted in a cost per LYG of £66,926 and a cost per QALY gained of £10,433.

Two-way sensitivity analyses were performed for the percentage weight loss experienced during the year of treatment, the utility gain for a 1 BMI unit drop, the calculated Framingham risk reductions and the calculated cost offsets for both CVD and diabetic therapies avoided. The analysis seems reasonably stable to these sensitivity analyses, with costs per QALY ranging from £8,433 to £16,000.

[More details commercial in confidence]

Discussion

Note: where possible, the mean difference between treatment and control groups is shown in terms of intention-to-treat analyses, and relates to a 120 mg tid dose of orlistat.

Clinical effectiveness

Most of the trials showed greater weight loss in orlistat groups versus placebo (statistically significant) at all endpoints,[37-43, 47] and results from several trials showed that orlistat was associated with better maintenance of weight loss.[41-44, 47] Findings from a small dose-ranging trial suggested that orlistat 120 mg tid was the optimum regimen in terms of weight loss.[37] This was supported by results of pooled analyses at one year.[41, 42, 46, 47] Pooled analysis of two small trials showed that orlistat within the dose range 50-60 mg tid did not produce weight loss that was significantly different from placebo at 12 weeks.[37, 38]

For non-diabetic participants at both 12 weeks and six months, the mean difference in favour of orlistat was approximately 1.7 kg.[37, 39] At one year the WMD from pooled analyses was 2.9 kg.[41, 42, 46, 47] For trials involving a one-year weight maintenance programme following a one-year weight loss regimen, the mean difference measured from baseline at the end of year two was 3.2 kg.[42, 47] For one trial evaluating a six-month weight loss regimen (diet only) followed by a one-year weight maintenance programme using orlistat, the mean difference calculated from the start of the weight loss phase was 1.3 kg in favour of orlistat.[44]

In obese patients with type-2 diabetes, orlistat 120 mg tid produced a statistically significant greater weight loss at one year compared with placebo (mean difference 1.8 kg). In addition, some parameters of glycaemic control and lipid concentration also showed a statistically significant greater improvement than placebo.[46] Orlistat also produced significant improvements in glycaemic control in non-diabetic participants.[41, 42] Three trials recruiting patients with various obesity-related risk factors showed statistically significant differences in favour of orlistat in terms of mean weight loss at one year. The mean difference range was 1.3-3.5 kg.[48-50]

Most trials showed statistically significant improvement in at least some lipid concentration parameters.[37, 40, 41, 43, 44, 47] Findings from one trial suggested that improvement in lipid levels was independent of weight loss.[41] However, another study showed no statistically significant between-group differences.[38] Results from three RCTs indicated that orlistat produced significant reductions in blood pressure relative to placebo.[43, 45, 47] One trial of patients with obesity-related risk factors found

[Commercial in confidence statements about lipid level profiles and indicators of glycaemic control,… DBP, total cholesterol and LDL-HDL ratio]

The distinction between statistical significance and clinical significance may be an important issue in orlistat trials. Many of the included RCTs demonstrated statistically significant differences between groups in terms of change in body weight in favour of orlistat. However, the mean difference between treatment groups was sometimes small, and it is possible that the differences observed were not clinically significant. This point may also apply to other outcomes (changes in lipid levels, indicators of glycaemic control, and blood pressure).

Adverse effects

The incidence of gastrointestinal adverse events was consistently higher in orlistat groups compared with placebo,[37, 39-47] and orlistat use was associated with lower serum levels of fat-soluble vitamins and / or a requirement for supplementation.[37, 39-42, 44, 46, 47] One dose-ranging study suggested that decreases in the serum levels of fat-soluble vitamins were dose-related.[39]

Health professionals should carefully consider the adverse effect profile associated with orlistat use, particularly in connection with gastrointestinal adverse effects. Some of the weight loss in orlistat-treated patients is probably explained by patients reducing their dietary fat intake in order to avoid symptoms such as fatty stools, increased defaecation, and oily spotting.[55] In most of the trials included in this review, it is reported that the majority of adverse effects were mild or moderate in intensity. It may be useful if qualitative research could be conducted in this area, to discover the meaning of these adverse effects from the patients' perspective, and to gain more information about patients' preferences for treatment.

Economic evaluations

Two economic evaluations were identified. One was a published DEC report in which the incremental cost utility of orlistat treatment was estimated as £45,881 per QALY gained (range: £19,452 to £55,391).[51] A second report (from company

submissions) estimated a cost per QALY gained for the general obese population as £10,433 (range £8,433 to £16,000).[52]

Possible explanations for the difference in outcomes for orlistat were considered. The assumptions relating to weight loss differed between the two reports. Weight loss was estimated as ***[Commercial in confidence]***during one year in the industry report,[52] and 3-4% (1.9% for people with type 2 diabetes) with weight regain in year two, in the DEC report.[51] The latter, more conservative estimate is more in line with the findings of this systematic review. Only one trial (with re-analysis) was chosen for efficacy data in the industry evaluation,[43] and it is unclear why other trials were not also considered.

[Further details commercial in confidence]

In the DEC report, utilities were calculated on the basis of the published trial results, however (as acknowledged by the DEC report authors) the data in the trials were not consistent with the EMEA prescription indications for orlistat. Therefore the cost/QALY gained figures obtained may be different from those obtained in clinical practice. In the trial used for clinical effectiveness data in the industry submission, patients were stratified according to weight loss after the 4 week run-in phase (<2 kg/>2kg), but all participants stayed in the trial.[43]

Limitations of the trials

In general, the methodological quality of included trials was moderate or good. Relatively few trials reported the use of methods to produce true randomisation. However, all the trials were described as 'double-blind' and were placebo controlled.

All included trials reported selection criteria for participants, reported group comparability at baseline, and expressed an intention to provide identical treatment to participants, apart from the drugs under study. Relatively few described the use of an *a priori* power calculation to estimate required sample size, and it is possible that

some trials lacked sufficient statistical power to detect statistically significant between-group differences for some outcomes.

Patients were blind in all trials by the use of identical placebo. It was less clear whether care-providers and outcome-assessors were also blind. In reality though, this is likely to be the case, since all trials were double-blind, and it is probable that provision of care and outcome assessment were carried out by the same staff. Due to the gastrointestinal adverse events that can occur with the use of orlistat,[55] there is the possibility that patients and study personnel may be able to guess that the active drug is being administered, and not the placebo. In two trials, this was highlighted as a potential problem.[38, 41] It is possible that study results could be biased if blinding is no longer valid. None of the trials included methods to determine the success of blinding of patients, care-providers, or outcome-assessors. In view of the potential difficulties involved, an assessment of the effectiveness of blinding would have been useful.

All trials described the statistical methods used for data analysis and most reported results in terms of a central value with associated variance. More than half of the trials described methods to deal with missing data, and most performed analyses based on intention-to-treat. Failure to use intention-to-treat analysis may cause bias brought about by non-random withdrawal of participants from the study.

Some trials that performed analysis by intention-to-treat employed the last observation carried forward (LOCF) method.[42, 47] This method involves filling in missing values by using the last observed value for that case, and therefore assumes that the outcome remains constant at the last observed value after withdrawal. Some problems have been identified with the use of this approach. If patients continue to take prescribed antiobesity medication after withdrawal, the LOCF is likely to underestimate the true treatment effect in those taking the active drug. If patients discontinue medication, and subsequently regain weight, the LOCF is likely to overestimate the true treatment effect.[57]

It has been suggested that analyses based on actual treatment received following withdrawal are of more value in explaining the biological effects of treatment. To this end, the multiple imputation model has been proposed, which involves analysis based

on treatment actually received after withdrawal as opposed to those to which participants were originally assigned. This involves a sensitivity analysis, incorporating imputations obtained for a range of alternative assumptions of dose after withdrawal. The range of assumptions include the following: continuation on same treatment as that immediately prior to withdrawal; reversion to control treatment after withdrawal; and assignment to treatment group dose that is the closest to the actual recorded dose after withdrawal. Ideally, trials should incorporate follow-up of withdrawals in order to record information on dosage received. Future trialists may wish to consider using the multiple imputation model as an alternative to the LOCF.[57]

Most trials reported numbers of withdrawals per group and with reasons. The majority of trials included an assessment of patient adherence with the trial regimen. However, this was usually based on counting returned capsules (drug regimen) or assessing food intake from patients' self-reported account (dietary regimen) and both methods are potentially unreliable.

Most of the trials included in this review comprise a single-blind, placebo, run-in period prior to double-blind treatment. Opinions differ as to the optimal approaches to analysis in trials of this type. One view is that the inclusion of weight loss occurring during the run-in period together with that achieved during double-blind treatment can be misleading, as it is the outcomes relating to the double-blind period which are the most important.[58] However, other experts claim that the run-in period is an important part of treatment as many risk-factor improvements occur during this time, and it should therefore be viewed as part of the whole treatment package.[59] Improved reporting and clarity in trials relating to whether statistical calculations take the start of the run-in period, or the start of double-blind treatment, as the starting point, would assist in interpretation of results.[60] One solution could be to report outcomes occurring during run-in separately to those for the double-blind period (starting from randomisation). Additional analyses could integrate outcomes during run-in and double-blind phases.

Generalisability of results

Use of orlistat in younger people

Since most of the trials included in this review stipulated a minimum participant age of 18 years, no information is available on the possible effects of orlistat in children and adolescents. Childhood obesity is an area of concern in the UK and other developed societies but has been more difficult to define and classify compared with adult obesity.[5, 26] However, a definition of overweight and obesity in children, based on pooled international data for BMI and linked to the adult obesity cut-off point of 30 kg/m^2, has recently been proposed by an expert working group.[61] Despite this progress, options to prevent and treat obesity in younger people remain relatively limited. The World Health Organisation (WHO) recommends that interventions in obese children should be designed to prevent weight gain rather than produce weight loss.[26] Another report emphasises the importance of a structured and multidisciplinary approach in this age group.[62] A previous systematic review found that family therapy and strategies to reduce sedentary behaviour may be promising interventions.[27] The issue of whether to use pharmacotherapy in childhood obesity is contentious. The Royal College of Physicians (RCP) does not recommend the use of antiobesity drugs in children due to lack of data about adverse effects on growth, development, and future eating behaviour.[31] Another source reflects the same concerns, but explains that further research may help to identify subgroups of younger people who may benefit from combining pharmacotherapy with dietary and physical activity modification.[63] During the course of this review, one clinical trial protocol was identified, involving the evaluation of orlistat in younger people with severe obesity (defined as BMI for age above 95th percentile according to National Health and Nutrition Examination Survey (NHANES) data). The population to be studied will comprise 12-17 year old African-American and Caucasian children and adolescents who have one or more obesity-related risk factors (hypertension, hyperlipidaemia, sleep apnoea, hepatic steatosis, insulin resistance, impaired glucose tolerance, or type-2 diabetes). Results of this clinical trial are awaited with interest. (See 'expiry date of review').

Use of orlistat in older people

Most of the trials included in this review focused on patients under 75 years of age, reflecting a lack of information on the effectiveness and safety of orlistat in older people. Despite the paucity of research in this age group, obesity is clearly an

important health problem in older age. In 1998, it was estimated that 48% of men in England aged 75 years and over were overweight and 16% were obese. The respective figures for women in the same age group were 37% and 20%.[4]

Two articles have highlighted pertinent issues around the use of pharmacotherapy in older people.[64, 65] Aspects to be taken into account when prescribing include impaired gastric absorption and motility, and the effects of altered body composition on drug distribution. As the individual ages, fat mass increases whilst fat-free mass reduces. These changes affect the absorption of drugs according to whether they are lipophilic (fat-soluble) or hydrophilic (water-soluble). The higher proportion of fat mass present in older people means that lipophilic drugs will have a higher distribution volume. In the case of hydrophilic drugs, although there is a smaller volume of distribution, the concentration achieved may be higher. Both of these phenomena can cause problems with drug toxicity meaning that the prescription regimen may need to be adjusted. In addition, impaired renal and hepatic function, and the high likelihood of concurrent morbidities and use of polypharmacy, producing the possibility of drug interactions, need to be considered when planning pharmacotherapy in older people.[64, 65] It is suggested that appropriate adjustment of drug regimens in older people can be achieved, but that attention should be paid to careful selection, dosing and monitoring in this age group. It is important that clinically significant effects, as distinct from those observed under controlled conditions, should be recognised.[65]

The possible effects of orlistat in the elderly have been considered and one area of concern may be the depletion of fat-soluble vitamins in a group who tend to already consume a sub-optimal level of vitamins and minerals.[64]

Although evidence exists to suggest that weight loss is beneficial to health,[20] a debate exists as to the usefulness and appropriateness of pharmacotherapy in obese elderly patients. One view is that weight loss in older people who are relatively fit and independent should not be encouraged. This is because weight loss leads to loss of fat-free mass as well as loss of fat mass, and this could contribute to lower levels of muscular strength and functional independence.[64]

Given the lack of research in this age group, and the fact that the elderly population in developed societies is increasing, further research on the clinical effectiveness and safety of orlistat in this group would be welcome.

Gender

The issues of gender differences in terms of obesity, and response to antiobesity treatment, is an area that may require further study. More men than women are overweight (46% versus 32% in England in 1998) but a slightly higher proportion of women than men are obese (19% versus 17% from the same survey).[4] Gender differences also occur in terms of fat distribution. Men tend to have more frequent central (abdominal) obesity, whilst thighs and buttocks are the commonest body areas for fat deposition in women. Of these two types of fat distribution, central obesity is more likely to be associated with hyperlipidaemia, coronary heart disease, hypertension, and impaired glycaemic control.[66] All of the included trials recruited participants of both sexes, and in general, there were larger proportions of female participants. None of the trials incorporated stratification of results according to gender. Future trials could usefully stratify results in this way to determine whether the treatment effects of antiobesity drugs are different between men and women.

Other demographic variables

It is possible that factors such as ethnicity and social class may also influence patients' response to treatment for obesity. Asian people are considered to be particularly at risk of developing obesity,[7] and, in general, the prevalence of obesity is inversely related to social class or household income, although this trend is more distinct in women.[4] Experts have not been able to offer a satisfactory explanation for the latter association.[5] Several of the trials included in this review reported the baseline distribution of different ethnic groups,[40-42, 44, 46] however, none presented results according to ethnic group, and none reported baseline distribution of social class or household income. It would be useful if future research could investigate the impact of treatment on different ethnic or social groups, in order to help determine the best patients to target for antiobesity pharmacotherapy.

Trials versus clinical practice

This review has identified some issues relating to the compatibility between trials and clinical practice in terms of patient characteristics and patient management.

Patient characteristics

In terms of patient characteristics, there are issues relating to methods for recruitment in clinical trials, and the relationship between selection criteria used in trials as opposed to those used to select patients for treatment in clinical practice.

In several of the included trials, the methods used for recruiting patients were not described. Recruitment methods involving advertising may attract participants who wish to lose weight for cosmetic reasons. Such trials may not reflect the use of anti-obesity drugs in patients with identified risk factors such as hypertension, impaired glycaemic control, and hyperlipidaemia, and may not be informative as to the effectiveness of drugs in improving risk factor profiles. Other recruitment strategies involve enlisting patients attending specialist obesity clinics. These patients may represent the most refractory cases, and may also underestimate the treatment effects which may be found in a more general population. It would be useful if future trials could incorporate selection criteria that reflect characteristics of people likely to be selected for treatment in clinical practice.

National prescribing guidelines state that orlistat should be used in the management of patients with a BMI of 30 kg/m^2 or more, or in those with a BMI of 28 kg/m^2 or more in the presence of other risk factors (i.e. hypertension, diabetes, hyperlipidaemia).[32] Of the 14 included trials, eight adhered to these guidelines,[40-42, 45, 46, 48-50] five had selection criteria allowing recruitment of patients not meeting the recommended criteria,[37, 39, 43, 44, 47] and in one it was unclear since inclusion criteria relating to baseline BMI were not provided.[38]

For orlistat trials that matched the recommendations, most reported statistically significant results in favour of the active drug relative to placebo in terms of weight loss for both diabetic[46] and non-diabetic participants,[40-42, 45, 48-50] and also produced statistically significant favourable results in terms of weight maintenance compared with placebo.[41, 42] One trial recruiting patients with type-2 diabetes also showed

statistically significant improvements in indicators of glycaemic control,[46] and a trial of non-diabetic participants showed improvements in blood pressure, glycaemic control, and some indicators of hyperlipidaemia in orlistat-treated patients relative to placebo.[41] However, findings for these outcomes from other trials were less clear.

It would be useful if future trials used participant inclusion criteria matched to recommended indications for drug use. Alternatively, baseline data and results could be stratified according to whether recruited patients met the recommended criteria or not.

Patient management

National prescribing guidelines indicate that treatment with orlistat should only be initiated in patients who have already achieved a weight loss of at least 2.5 kg in four weeks using a dietary programme alone,[32, 33] and that treatment should be discontinued after 12 weeks in patients who lose less than 5% of body weight as measured from the start of drug therapy.[33] European prescribing guidelines also reflect these recommendations and state that the duration of treatment with orlistat should not be longer than two years.[34]

Most of the orlistat trials included in this review incorporated a four-week, single-blind, placebo run-in period, during which time patients were instructed to follow a hypocaloric diet (precise parameters vary slightly between trials). It may be considered that this phase loosely corresponds to the requirement in clinical practice for patients to undergo a four-week period of treatment involving dietary modification (albeit without placebo) in an attempt to lose at least 2.5 kg prior to treatment with orlistat. However, weight loss during the run-in period was not always reported in the trials, and was not used as an eligibility criterion for orlistat treatment, with three exceptions. In one trial, it was stipulated that patients had to lose between 0.5 and 4 kg during the run-in in order to progress to double-blind treatment,[38] and in another, by the same research group, the criterion was loss of 0-4 kg during the run-in (however, this includes no weight loss at all).[37] In a third trial, patients were required to lose at least eight percent of initial body weight during a six-month run-in period using diet alone, in order to be eligible to participate in a double-blind trial of weight maintenance therapy.[44] Most of the trials did not report proportions of patients losing

at least five percent of body weight (measured from the start of randomisation) at 12 weeks, and none used failure to achieve this as a rationale for discontinuing treatment. It is possible that future trials could match the recommended prescription indications more closely in one of two ways.

First, a protocol could be established to withdraw treatment in patients who fail to lose at least five percent of body weight measured after 12 weeks of double-blind treatment. Therapy could then be continued in successful cases. In terms of the general use of antiobesity drug therapy, RCP recommendations also reflect the principle of discontinuing treatment in patients who have not lost at least 5% body weight at 12 weeks. A further recommendation relating to those who are successful in achieving this outcome, is that drugs may be continued beyond this initial period, provided body weight is continually monitored and weight is not regained.[31] This pattern of care could be reflected in trials.

An alternative approach may be for trials to report rates of at least five percent loss at 12 weeks, retain the patients who fail to achieve this, and thereafter stratify results according to success or failure of this outcome. Trials should also try to match the pre-treatment phase, and withdraw those not losing 2.5 kg during the run-in period, if they are to correspond with the scheme proposed in the licensing indications.

It is apparent that management of patients recruited for trials does not closely correspond to management of patients in clinical practice. It is likely that management of patients in the placebo arm of trials represents more intensive management than is normally seen in usual clinical practice. For example, patients attend clinic more often, and receive closer dietary supervision in trials. Although placebo-controlled RCTs, in which all participants receive identical treatment with the exception of the study medication, should give an indication of the effects of the active drug over and above the rest of the treatment package and the placebo effect, it may be useful if future trials could try to replicate management of patients in everyday clinical practice, and attempt to assess the effectiveness of anti-obesity drugs combined with usual clinical management over and above usual clinical management without drugs.

For most obese people, obesity is a chronic condition, with a tendency to experience patterns of weight loss and weight regain over time. In light of this, longer-term data on the effectiveness and safety of orlistat would be helpful. The maximum recommended prescription duration for orlistat is two years.[34] Several trials included in this review involve evaluation of two years' use with orlistat (i.e. a one-year weight loss programme followed by a one-year weight maintenance programme),[41-43, 47] but no data were identified beyond this point.

Sponsorship of trials

It should be noted that most of the trials included in this review were described as being sponsored by the manufacturer. In one case, the sponsorship was unclear, but it was apparent that the trialists had a connection with the drug company.[42]

Comparison with other systematic reviews

One other comparable systematic review of effectiveness was identified, prepared as a Development and Evaluation Committee (DEC) report, which evaluated the effectiveness and safety of orlistat in the treatment of obesity.[51] Several differences were noted between this and the current review. First, only four electronic databases were searched: MEDLINE, EMBASE, The Cochrane Library, and the Internet (Alta Vista), whereas the current review included searches of 19 different electronic databases plus Internet searches. Few details of the review process were provided in the DEC report, for example, screening tools for papers, the number of reviewers involved in study selection and appraisal, independence of decision-making, and methods for resolving disagreements were not reported. In the DEC report, inclusion criteria for trials were not described in detail and there was no structured presentation of assessment of methodological quality of included trials, although certain quality-related aspects were discussed, such as use of the intention-to-treat protocol. Three trials were included, which have also been included in the current review.[41, 43, 46] The current review included 11 published trials of orlistat, however several of these will have been published after the completion of the DEC report. It appears that the DEC report excluded shorter term trials from the systematic review,[37-39] however, this was not explained as an exclusion criterion, and details of shorter term trials were shown in appendices, in tables of adverse effects. An economic analysis was also included in the DEC report and this has already been discussed. The main conclusions from the

DEC report were: (1) whilst orlistat promotes weight reduction for some people in the short term, discontinuation of treatment results in weight regain; (2) the protocols of the trials included in the review do not coincide with the licensed indication for orlistat and so generalisability is limited; and (3) there is a lack of long-term data on the effectiveness and safety of orlistat use.

Conclusions

Implications for future research

In general, the methodological quality of included trials was moderate or good. However, possible difficulties with maintenance of blinding were identified. This is an important consideration as both the patient and the investigators may be able to recognise the use of orlistat due to associated gastrointestinal adverse effects. It would be useful if future trials could attempt to assess the effectiveness of blinding in patients and those assessing outcomes. It is recommended that intention-to-treat analysis is incorporated into future trials, however the optimum methods for achieving this are under debate.

Further research is required in younger and older patients to assess the effects of orlistat in these age groups. In addition, results could usefully be stratified by variables such as gender, ethnicity, and social class in order to assist clinicians in identifying the types of patients most likely to benefit from treatment. In order to assist with generalisability of results, patient selection in trials should match the criteria for treatment in clinical practice, and trials should be structured to correspond with recommended treatment protocols for orlistat.

Implications for clinical practice

Many of the trials included in this review demonstrated statistically significant differences between groups in terms of absolute weight loss, proportions of patients achieving at least 5% or 10% loss of initial body weight, and weight maintenance, in favour of orlistat, when compared with placebo. Sometimes the mean difference between treatment groups was small, and health care professionals involved in the

care of obese patients will need to decide whether these differences are clinically significant. In addition, the possibility of adverse effects in orlistat-treated patients should be taken into account. The optimum regimen was 120 mg tid. Between group differences in other outcomes (changes in lipid levels, indicators of glycaemic control, and blood pressure) were less consistent across trials in terms of statistical significance. In studies where the between-group difference for these outcomes was statistically significant, clinicians should judge whether the differences observed were of clinical importance.

Two economic evaluations generated differing values for cost per QALY (£10,433 and £45,881). However, the lower figure was based on an assumption for weight loss that may have been inaccurate. Assumptions used in the calculation of the higher value correspond with the evidence identified in this review.

Conflicts of interest

Dr Susan Jebb, a member of the advisory panel, has in the past been a member of the Roche Medical Advisory Board and has undertaken industrial consultancy and educational projects on behalf of Roche.

Professor Peter Kopelman, a member of the advisory panel, has undertaken clinical trials in obese participants for Roche.

Expiry date

Forthcoming research:

(1) Identified from the National Research Register (NRR) as an ongoing trial:

Title: clinical trial of orlistat – a pancreatic lipase inhibitor
Start date: 01/11/1999. End date: 01/11/2001.
Lead researcher: Professor R. L. Kennedy, Department of Medicine, Sunderland Royal Hospital, Kayll Road, Sunderland, SR4 7TP.

(2) Identified from internet searches as a clinical trial protocol:

Title: Protocol number: 98-CH-0111

Safety and efficacy of orlistat in African American and Caucasian children and adolescents with obesity-related comorbid conditions.

Start date: 2000. End date: 2003

Lead researcher: Dr Jack Yanovski, Developmental Endocrinology Branch, NICHD, NIH, Bethesda, Maryland 20892-1862, USA.

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Appendix 1: Expert panel

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Appendix 2: Search strategy

The search strategy below was used for the joint review of orlistat and sibutramine:

#1	explode "Obesity"/ all subheadings
#2	"Body-Weight"/ all subheadings
#3	"Hyperphagia"/ all subheadings
#4	"Adipose-Tissue"/ all subheadings
#5	weight or overweight or obese or obesity or antiobesity
#6	food or appetite or satiety
#7	adiposity or overeating
#8	hyperphagia or fat
#9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10	orlistat
#11	xenical
#12	tetrahydrolipstatin
#13	sibutramine
#14	meridia in ti,ab
#15	#10 or #11 or #12 or #13 or #14
#16	#9 and #15

This strategy was used for the MEDLINE database and was adapted as appropriate for the other databases searched.

Appendix 3: Prescreen form

(1) Paper (author & year)

(2) Study design (eligible for inclusion: RCT)

(3) Participants (eligible for inclusion: overweight / obese or maintaining weight loss)

(4) Interventions (eligible for inclusion: orlistat)

(5) Outcomes (eligible for inclusion: body weight, fat content, or fat distribution assessed at both baseline and post-intervention)

(6) Language (eligible for inclusion: English, French, German, Dutch)

(7) Decision:

Appendix 4: Data extraction tables for RCTs

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Drent & van der Veen (1993)[38] Netherlands Aim To investigate the additional weight reducing potential and tolerability of orlistat in obese patients receiving dietary treatment Method of randomisation Not stated Outcomes Change in body weight; dietary intake (assessed from diaries); BP; heart rate; adverse events; adherence with drug regimen (assessed by counting number of returned capsules); vitamin A and E levels; lipid levels; ECG; haematology; blood chemistry; urinalysis. Setting and length of treatment Outpatients. 4 week run-in. 12 week DB treatment phase	Population Volunteers, responding to an advertisement in the local newspaper Inclusion criteria For run-in Obese but otherwise healthy outpatients; age 18-55 years; body weight 20-50% above ideal according to 1983 Metropolitan Life Insurance Tables For DB study Adherence with the dietary regimen during run-in (defined as body weight reduction of 0.5-4 kg during run-in, and by completion of diaries); adherence with the drug regimen (assessed by counting placebo capsules; at least 80% used) during run-in Exclusion criteria GI disorder; use of laxatives or drugs that could affect body weight	4-week, SB, placebo run-in period for all patients The basal calorific requirement was calculated for each patient according to gender, age and actual weight. The calculated daily intake was multiplied by 1.3 to adjust for mild to moderate daily activities, then reduced by 500 to obtain weight loss. Patients were instructed to follow this 500 kcal-reduced diet containing 30% calories as fat, and to complete a diary recording their dietary intake, physical activities and defaecation pattern. All received placebo capsules tid with main meals. (n=52) Standard care for all patients during DB phase Dietary regimen as above C: Placebo capsules tid (n=21) I: Orlistat 50 mg tid (n=23)	Gender no. m/f C: 3/16 I: 3/17 Mean±sd age (years) C: 41.6±8.2 I: 41.9±8.1 Mean±sd weight (kg) C: 81.9±7.9 I: 85.5±12.1 Mean±sd BMI (kg/m^2) C: 30.0±2.6 I: 30.6±3.7 Patients were normolipidaemic at baseline, and vitamin A and E levels within the range of reference values	Statistical techniques ANOVA with repeated measurements and unpaired and paired t tests Weight loss mean±sd during run-in Overall: 2.63±1.08 kg C: 2.61±1.17 kg I: 2.65±1.01 kg Weight loss mean±sd between randomisation and end of 12 week DB treatment period C: 2.1±2.8 kg I: 4.3±3.4 kg 95% CI for the difference in weight loss was 0.2, 4.2 kg Cardiovascular changes Cholesterol and triglyceride levels did not change. There were no significant changes in BP, heart rate, biochemical or haematological parameters in either group	Withdrawals C: 2 motivation problems I: 3 (1 non-adherence with diet; 1 dissatisfaction with amount of weight lost; 1 adverse events, including some episodes of faecal incontinence) No. with GI adverse events Abdo pain C: 4 I: 12 Liquid stools C: 1 I: 8 Faecal incontinence C: 0 I: 2 Urgency C: 0 I: 1 Oily stools C: 0 I: 3 Nausea C: 0 I: 5 Vomiting C: 1 I: 4 Flatulence C: 2 I: 5 Haemorrhoids C: 0 I: 1 Most GI events were mild or moderate The incidence of adverse events (other than GI) was not significantly different between groups Vitamin A & E levels For most patients, levels remained within reference values during the study	Limitations of study, as noted by study authors Although the study was DB, the adverse events enabled some patients to guess that they received orlistat, especially when complaints were more than mild Sponsorship Hoffmann-La Roche

Abbreviations: BP – blood pressure, DB – double blind, GI – gastrointestinal, SB – single blind, I – intervention group, C – control group, sd – standard deviation, tid – three times per day, no. – number, m – male, f – female, BMI – body mass index, ANOVA – analysis of variance, 95% CI – 95% confidence interval, abdo – abdominal.

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Drent et al (1995)[37] Netherlands/Denmark/Germany /Sweden Aim To evaluate the efficacy and tolerability of orlistat in doses of 10, 60 and 120 mg tid in addition to a mildly hypocaloric diet Method of randomisation Method of randomisation not stated. Patients stratified according to gender Outcomes Change in body weight; anthropometry; vital signs; adverse events; serum lipid levels; serum levels of vitamins A, D, and E; adherence with dietary regimen Setting and length of treatment Multicentre study involving 5 clinics in Denmark, The Netherlands, Germany, and Sweden. 4 week run-in followed by 12 week DB study	Population Not stated Inclusion criteria For run-in phase Obese, otherwise healthy; age 25-60 years; BMI 27.8 – 35.0 kg/m^2 for men and 27.3 – 35.0 kg/m^2 for women; waist-to-hip ratio ≥0.9 for men and ≥0.8 for women; accustomed to 3 main meals per day; consistent regular physical activity; women to be surgically sterile, 1 year postmenopausal, or using reliable mechanical contraceptives For DB phase Patients adhering to the dietary regimen (defined as body weight reduction of 0-4 kg and a deviation of less than 20% from prescribed intake of total calories and calories as fat in 3 out of 4 day calculations from dietary records) and adhering to the drug regimen during run-in (assessed by counting placebo capsules, at least 80% should have been used) were randomised to DB phase	4-week, SB, placebo run-in period for all patients The basal calorific requirement was calculated for each patient according to gender, age and actual weight. The calculated daily intake was multiplied by 1.3 to adjust for mild to moderate daily activities. The energy intake was estimated from 4-day dietary records. The average estimated energy requirement was then reduced by 500 kcal in order to obtain weight loss. Patients were instructed to follow this 500 kcal-reduced diet containing 30% calories as fat, and to complete a dietary diary during the whole 16 week study period. All received placebo capsules tid with main meals. (n=237) Standard care for all patients Dietary regimen as above. At all clinic visits diet diaries were discussed with the dietician. C: Placebo tid (n=46) I1: Orlistat 10 mg tid (n=48) I2: Orlistat 60 mg tid (n=45) I3: Orlistat 120 mg tid (n=47)	Gender no. m/f C: 18/28 I1: 21/27 I2: 20/25 I3: 20/27 Mean±sd age (years) C: 43.4±8.5 I1: 44.9±9.2 I2: 43.5±8.4 I3: 44.6±9.3 Mean±sd weight (kg) C: 90.0±11.6 I1: 92.1±12.3 I2: 92.6±12.5 I3: 94.1±12.9 Mean±sd BMI (kg/m^2) C: 31.1±2.1 I1: 31.5±2.2 I2: 31.5±2.3 I3: 31.4±2.5 Waist-hip ratio C: 0.91±0.07 I1: 0.93±0.07 I2: 0.92±0.07 I3: 0.94±0.06	Statistical techniques ANOVA and ANCOVA. Safety population analysis included those who had received at least one dose of medication after randomisation; ITT analysis as above plus at least one body weight measurement performed; standard efficacy analysis included those adhering to drug and dietary regimens for at least 4 weeks of randomised treatment. For ITT and standard efficacy analyses, the last available body weight was used as a week-12 value. Mean±sem weight change (kg) at 12 weeks adjusted for weight loss during run-in ITT analysis C: -2.98±0.38 I1: -3.61±0.38 I2: -3.69±0.39 I3: -4.74±0.38 P=0.001 C vs I3, other comparisons n.s. Standard efficacy analysis C: -3.20±0.42 I1: -3.64±0.45 I2: -3.85±0.44 I3: -4.76±0.41 P=0.009 C vs I3, other comparisons n.s. Mean±sd change in total cholesterol after 12 weeks. ITT analysis adjusted for baseline levels (mmol/l) C: 0.22±0.55 I1: 0.10±0.73 I2: -0.10±0.67 I3: -0.22±0.53 n.s. C vs I1, p=0.011 C vs I2, p=0.001 C vs I3	Withdrawals: safety population GI adverse events (numbers) C: 0 I1: 0 I2: 0 I3: 3 Circumoral paresthesia C: 0 I1: 1 I2: 0 I3: 0 Asthenia C: 0 I1: 0 I2: 0 I3: 1 One patient suffered from both GI complaints and asthenia Reasons other than A/E C: 6 I1: 4 I2: 3 I3: 2 Total withdrawals C: 6 I1: 5 I2: 3 I3: 5	Study limitations as noted by the study authors Patients may under-report their food intake in the diet diaries. However, this should be the case across all treatment groups Sponsorship Roche

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
	Exclusion criteria Hx cardiac disease requiring medication; oedema of non-cardiac origin; hx of drug hypersensitivity or allergic conditions which may interfere with the study; transaminases 100% above upper reference value; serum creatinine >160µmol/l, proteinuria >500 mg/dl; use of drugs influencing body weight and serum lipid or vitamin levels; Cushing's syndrome, diabetes mellitus requiring drug treatment or other endocrine abnormalities other than 1-thyroxine-stabilised hypothyroidism; hx of substance abuse; hx of GI disorders, pancreatitis, pancreas lipase deficiency or lactose intolerance; hx of eating disorders; any abnormality of potential clinical significance		Total cholesterol (mmol/l) C: 5.5±0.8 I1: 5.6±1.0 I2: 5.6±1.0 I3: 5.6±1.1 LDL cholesterol (mmol/l) C: 3.7±0.7 I1: 3.6±0.7 I2: 3.8±0.8 I3: 3.9±1.1 Triglycerides (mmol/l) C: 1.5±1.7 I1: 2.1±2.4 I2: 1.5±1.1 I3: 1.6±0.9	Mean±sd change in LDL at 12 weeks ITT analysis adjusted for baseline levels (mmol/l) C: 0.13±0.39 I1: 0.14±0.68 I2: -0.14±0.42 I3: -0.19±0.51 n.s. C vs I1, p=0.012 C vs I2, p=0.003 C vs I3 Mean±sd change in LDL/HDL ratio after 12 weeks. ITT analysis adjusted for baseline levels C: -0.07±0.63 I1: 0.02±0.62 I2: -0.13±0.60 I3: -0.39±0.71 n.s. C vs I1, n.s. C vs I2, p=0.033 C vs I3 Mean±sd change in triglycerides after 12 weeks. ITT analysis adjusted for baseline levels (mmol/l) C: 0.05±0.94 I1: -0.36±1.44 I2: 0.03±0.65 I3: -0.20±0.61 n.s. C vs I1, C vs I2, C vs I3 Mean±sem change in serum levels of vitamin A total after 12 weeks. ITT analysis (µmol/l) C: -0.034±0.059 I1: -0.004±0.059 I2: -0.042±0.059 I3: -0.095±0.058		

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
				Mean±sem change in serum levels of vitamin D total after 12 weeks. ITT analysis (nmol/l) C: -15.4±3.7 I1: -12.1±3.8 I2: -23.3±3.8 I3: -13.8±3.7 Mean±sem change in serum levels of vitamin E total after 12 weeks. ITT analysis (µmol/l) C: 0.81±0.91 I1: -0.69±0.91 I2: -3.16±0.91 I3: -3.48±0.89 P<0.01 C vs I2 and C vs I3 Adverse events Mild to moderate adverse events were common in the orlistat groups, particularly at the 2 higher doses. Severe (very inconvenient) events were observed in small percentages of patients, again at the 2 higher doses Adherence with dietary regimen Information from diet diaries indicated that patients adhered to the dietary regimen		

Abbreviations: tid – three times per day, DB – double blind, BMI – body mass index, hx – history, SB – single blind, C – control group, I1 – first intervention group, I2 – second intervention group, I3 – third intervention group, no. – numbers, m – male, f – female, sd – standard deviation, LDL – low density lipoprotein, ANOVA – analysis of variance, ANCOVA – analysis of covariance, ITT – intention-to-treat analysis, sem – standard error of the mean, n.s. – not significant, vs – versus, HDL – high density lipoprotein, GI – gastrointestinal, A/E – adverse events.

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Micic et al (1999)[45] Yugoslavia Aim To investigate the effect of orlistat on weight reduction and serum lipid levels, and to assess tolerability. Method of randomisation Not stated Outcomes Body weight; sitting BP, heart rate; serum lipid levels; standard laboratory tests for blood and urine; adverse events; patient adherence Setting and length of treatment Endocrinology centres in Yugoslavia. 2 week run-in, followed by 24 week DB trial.	Population Not stated Inclusion criteria For run-in Age 18-75 years; BMI ≥30 kg/m^2; serum LDL-cholesterol ≥4.2 mmol/l; if female – use of adequate contraception, surgically sterile or post-menopausal For DB phase Unclear. Adherence with run-in regimen?	2 week, SB, placebo run-in period for all patients Commenced mild hypocaloric diet, individually determined, deficit 600 kcal/day, but no less than 1200 kcal/day. Placebo bd. (n=120) Standard care for all patients during DB study Continued dietary regimen as above. C: Placebo tid with main meals for 24 weeks (n=59) I: Orlistat 120 mg tid with main meals for 24 weeks (n=60)	Gender no. m/f C: 13/46 I: 18/42 Mean±sd age (years) C: 43.95±10.72 I: 45.47±8.06 Mean±sd weight (kg) C: 97.67±6.13 I: 100.3±20.2 Mean±sd BMI (kg/m^2) C: 36.28±5.23 I: 36.08±6.25 Study authors stated that there were no statistically significant differences between groups in terms of lipid levels, vital signs, and serum and urine laboratory tests.	Statistical techniques Two-sided tests used for all analyses. Chi-square, Mann-Whitney, Fischer, McNemarov, t-test for dependent samples, t-test for independent samples, repeated measures ANOVA (with and without factor-therapeutic group), regression. Number (%) patients with weight loss/gain after 4 weeks of therapy C: 41 (73.2%) / 15 (26.8%) I: 53 (91.4%) / 5 (8.6%) P<0.05 Number (%) patients with weight loss/gain after 24 weeks of therapy C: 43 (87.8%) / 6 (12.2%) I: 50 (100.0%) / 0 (0.0%) P<0.05 Mean (%) weight loss at 24 weeks C: 7.34 kg (7.5%) I: 10.75 kg (10.7%) P-value not reported Number (%) patients with BMI reduction of <4 kg/m^2 at 24 weeks C: 31 (72.1%) I: 26 (52.0%) n.s. Number (%) patients with BMI reduction of 4-12 kg/m^2 at 24 weeks C: 12 (27.9%) I: 24 (48.0%) P<0.05	One patient withdrew during the run-in Ten patients from each study group withdrew during the DB treatment. Overall withdrawal 16.8% Reasons for withdrawal C/I Irregular visits 0/1 Contact lost 1/1 Adverse event 0/1 Patient's decision 9/6 Protocol violation 0/1 Completers C: 49 I: 50 Numbers (%) available for analysis of efficacy and tolerability C: 56/59 (95%) I: 58/60 (96.7%) Not available for analysis of efficacy C: 0 I: 2 (3.3%) Not available for analysis of efficacy or tolerability C: 3 (5%) I: 0 Number of patients (%) with adverse events/new disease C: 7/59 (11.9%) I: 18/60 (30.0%) No. with GI adverse events C: 11 I: 29 No. with oily stools C: 8 I: 27	Limitations of the study, as noted by the study authors None stated Sponsorship Hoffman-La Roche

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
	Exclusion criteria Total serum triglycerides >4.5 mmol/l; pregnancy; lactation; of childbearing potential not using adequate contraception; hx of the following during 6 months prior to screening: MI, CABG, coronary angioplasty; significant cardiac, respiratory, renal, neurological, GI or endocrine disease that may have an impact on study parameters or safety; hx of GI surgery for weight loss; hx of post-operative adhesions; active GI disease; pancreatic disease; type 2 diabetes mellitus; proliferative retinopathy and clinical nephropathy; hx or presence of cancer (except successfully treated skin or cervical cancers); hx or presence of bulimia or laxative abuse; abnormal laboratory values that are 100% above reference range; fat soluble vitamin deficiencies; received investigational new drug within last 3 months; hx of psychological illness or condition that may interfere with the patient's ability to understand the study requirements; use of appetite suppressants, fish oil supplements, retinoids, systemic steroids, anticoagulants, acarbose (2 month wash-out period prior to randomisation required).			Changes in serum lipid levels Total cholesterol reduction C: 5.9% I: 13.9% LDL-cholesterol reduction C: 5.9% I: 19.4% HDL-cholesterol change C: decreased by 2.54% I: increased by 0.95% LDL/HDL ratio reduction C: 5.3% I: 20.3% Total triglycerides change C: increased by 7.10% I: decreased by 5.32% p-values not reported for analysis of lipid levels, however authors state that between group differences were statistically significant Vital signs and laboratory tests Sitting SBP in I patients showed significant reductions throughout the trial (p=0.05 at 24 weeks). No significant change in C. Sitting DBP in I patients showed significant reductions throughout the trial (p=0.001 at 24 weeks), and in C patients after week 20 (p=0.008 at week 24). There was no statistically significant difference between I and C in mean values of SDP and DBP. Analysis of heart rate, ECG, and laboratory tests showed no significant differences within groups over time, or between groups.	No. with other adverse events Depression C: 1 I: 0 Discopathy C: 1 I: 0 Headache C: 0 I: 1 Breast abscess C: 0 I: 1 Tonsillitis C: 1 I: 0 In one I patient, oily stool with diarrhoea led to interruption of therapy. Intensity of adverse events was usually mild to moderate. Patient adherence with drug regimen (assessed by counting returned capsules) Adherence was around 90% in both groups (this was considered satisfactory)	

Abbreviations: bd – twice per day, tid – three times per day, DB – double blind, BMI – body mass index, hx – history, SB – single blind, C – control group, I –intervention group, no. – numbers, m – male, f – female, sd – standard deviation, LDL – low density lipoprotein cholesterol, ANOVA – analysis of variance, n.s. – not significant, HDL – high density lipoprotein cholesterol, GI – gastrointestinal, BP – blood pressure, SBP – systolic blood pressure, DBP – diastolic blood pressure, MI – myocardial infarction, CABG – coronary artery bypass grafting.

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Van Gaal (1998)[39] Austria, Belgium, Brazil, Finland, Germany, Italy, Sweden, Switzerland, UK Aim To determine the weight-reducing efficacy and tolerability of orlistat, and to define the optimal dosage regimen Method of randomisation Not stated Outcomes Change in body weight; vital signs; ECG; adverse events; clinical chemistry; haematology; serum levels of vitamins A, D, E, and beta-carotene; urinalysis; waist and hip circumference; faecal fat excretion; plasma levels of orlistat; gallbladder ultrasound; adherence with drug regimen (assessed by counting the number of returned capsules at clinic visits); adherence with dietary regimen (assessed with diet diaries) Setting and length of treatment 14 centres located in Austria, Belgium, Brazil, Finland, Germany, Italy, Sweden, Switzerland, and the UK. 4 week run-in followed by 24 week DB phase.	Population Not stated Inclusion criteria For run-in Age ≥18 years, BMI 28-43 kg/m^2; women of childbearing potential eligible if using adequate contraceptive measures For DB phase At least 70% adherence with drug regimen during run-in; no proven evidence of multiple gallstones (assessed by ultrasound) or symptomatic cholelithiasis; lipid-soluble vitamin levels within the clinical reference range; no clinically significant GI disorder	4 week, SB, placebo run-in period for all patients Nutritionally balanced hypocaloric diet, designed to result in weight loss of 0.25-0.5 kg per week, containing 30% calories as fat, 50% as carbohydrate, 20% as protein, and maximum cholesterol 300 mg/day. Total daily energy expenditure estimated for each patient from the basal metabolic rate multiplied by 1.3 to account for mild to moderate activity levels. Minimum prescribed calorie intake was 1200 kcal/day, deficit was 600 kcal/day. If BMI recorded as ≤22 kg/m^2 on 2 consecutive visits, prescribed calories were increased to maintain weight. Placebo tid. (n=676) Standard care for all patients during DB study Dietary regimen continued as above. C: Placebo tid with main meals (n=123) I1: Orlistat 30 mg tid with main meals (n=122) I2: Orlistat 60 mg tid with main meals (n=123) I3: Orlistat 120 mg tid with main meals (n=120) I4: Orlistat 240 mg tid with main meals (n=117)	Gender % male C: 22% I1: 25% I2: 24% I3: 21% I4: 25% Mean±sd age (years) C: 43±11 I1: 40±11 I2: 42±11 I3: 40±11 I4: 44±11 Mean±sd BMI (kg/m^2) C: 35±4 I1: 35±4 I2: 34±4 I3: 35±4 I4: 34±4	Statistical techniques Safety analyses included those who had received at least one dose of trial medication after randomisation and had a subsequent safety observation. ITT analyses included those who had received at least one dose of study medication and had a subsequent efficacy observation. Null hypothesis tested using ANOVA and ANCOVA. For each centre the placebo adjusted 95% CI of orlistat effect (based on LSM) was calculated, and the placebo-adjusted LSM differences from each centre were used in the Michaelis-Menton model to assess the dose-response relationship. Diet diaries There were no differences between groups with respect to energy or fat consumption. Weight loss during run-in All treatment groups lost similar amounts of weight (approx 3 kg) Mean % weight loss at 24 weeks in relation to initial weight C: 6.5% I1: 8.5% I2: 8.8% I3: 9.8% I4: 9.3%	Withdrawals during run-in Overall 63/767 (9%) Most common reasons: Entry violation 13 patients Lost to F/U 12 patients Uncoop 11 patients A/Es 8 patients % withdrawals during DB treatment C/I1/I2/I3/I4 Refused treatment 8% / 7% / 7% / 3% / 5% Adverse events 2% / 6% / 5% / 2% / 3% Lost to follow-up 7% / 6% / 6% / 7% / 5% Uncooperative 1% / 3% / 2% / 3% / 4% Administrative 2% / 2% / 3% / 3% / 0 Protocol violation 1% / 1% / 1% / 1% / 0 Entry violation 0 / 0 / 0 / 1% / 0 Total 22% / 24% / 23% / 19% / 17% Patients with A/Es C: 69% I1: 79% I2: 83% I3: 84% I4: 87% Most A/Es were mild to moderate in nature. With the exception of GI events, they were judged to be mostly unrelated to treatment Patients with GI A/Es C: 46% I1: 61% I2: 76% I3: 71% I4: 83%	Limitations of the study, as noted by the study authors None stated Sponsorship Hoffman-La Roche

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
	Exclusion criteria Weight loss >4 kg in the 3 months before screening; hx or presence of significant medical disorders, including diabetes mellitus, cardiovascular disease, uncontrolled hypertension, and pancreatic disease; previous GI surgery for weight reduction; hx of post-operative adhesions; hx or presence of cancer (with exception of treated basal cell carcinoma); psychiatric or neurological disorders requiring chronic medications or liable to prejudice patient adherence; evidence of alcohol or substance abuse; bulimia or laxative abuse; pregnancy or lactation; post-menopausal women who had been amenorrhoeic for less than 1 year; use of drugs capable of influencing body weight or plasma lipids during the month prior to study entry; concomitant use of anticoagulants, digoxin, anti-arrhythmics and lipid-soluble vitamin supplements.			LSM differences from placebo at 24 weeks (body weight) I1: 0.95 kg I2: 1.86 kg I3: 2.55 kg I4: 2.81 kg p≤0.002 C vs I2, p≤0.001 C vs I3, p≤0.001 C vs I4 Patients losing more than 10% initial body weight C: 19% I1: 28% I2: 28% I3: 37% I4: 38% Mean change in waist circumference C: -3.5 cm I1: -5.1 cm I2: -5.9 cm I3: -6.3 cm I4: -6.0 cm Mean change in daily faecal fat excretion C: -0.1 g I1: +11.5 g I2: +15.4 g I3: +18.5 g I4: +23.5 g Pharmacokinetics Analysis of plasma samples confirmed that the overall absorption of orlistat was very low	No. with severe GI A/Es C: 1 I1: 9 I2: 8 I3: 2 I4: 10 Most of the orlistat treated patients experienced 1 or 2 episodes of GI events, generally within the first few weeks of initiating treatment. Most episodes were mild to moderate in severity. 3 patients (2%) in C and 18 patients (4%) in the orlistat groups withdrew due to various A/Es. 11 patients withdrew due to GI events, 10 of whom were treated with orlistat. Withdrawals due to A/Es related to treatment C: abnormal GTT, urticaria I1: faecal incontinence, flatulence, liquid stools, abdominal pain, polymyalgia rheumatica I2: abdominal pain, depression I3: gastritis, liquid stools I4: faecal incontinence Serious A/Es were reported by 2 patients in C and 12 patients in the 4 orlistat groups. 4 were considered as possibly related to treatment (faecal incontinence, diverticulitis I1; abdominal pain I2 and I4). All patients apart from the one in I4 withdrew.	

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
					No clinically relevant abnormalities related to orlistat were found in laboratory values, hepatocellular damage, vital signs, ECG. There was no evidence to support notion of increased cholelithiasis. <u>Patients with low levels of fat-soluble vitamins on 2 or more consecutive occasions</u> C: 3.3% I1: 4.2% I2: 6.7% I3: 4.2% I4: 12.8% <u>No. patients who received supplemental fat-soluble vitamins</u> C: 2 I1: 2 I2: 0 I3: 4 I4: 8 There were statistically significant differences between the levels of vitamin D (I4 only), E and beta-carotene in C and orlistat treated groups at 24 weeks (LSM difference p≤0.001).	

Abbreviations: tid – three times per day, DB – double blind, BMI – body mass index, hx – history, SB – single blind, C – control group, I1 – first intervention group, I2 – second intervention group, I3 – third intervention group, I4 – fourth intervention group, no. – numbers, sd – standard deviation, ANOVA – analysis of variance, ANCOVA – analysis of covariance, ITT – intention-to-treat analysis, vs – versus, GI – gastrointestinal, A/E – adverse events, 95% CI – 95% confidence intervals, LSM – least squares mean, F/U – follow-up, uncoop – patient did not co-operate.

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Hollander et al (1998)[46] USA Aim To determine the efficacy of orlistat when used in obese patients with type 2 diabetes in terms of weight loss, glycaemic control and lipid status Method of randomisation Method not stated. Stratification according to weight loss and glucose control during run-in. First stratum: weight loss ≤2.0 kg, glucose 5.6-8.9 mmol/l. Second stratum: weight loss ≤2.0 kg, glucose 9.0-12.2 mmol/l. Third stratum: weight loss >2.0 kg, glucose 5.6-8.9 mmol/l. Fourth stratum: weight loss >2.0 kg, glucose 9.0-12.2 mmol/l. Outcomes Change in body weight; glycaemic control; lipid levels; waist circumference; standard laboratory measurements (haematology, clinical chemistry, urinalysis, faecal occult blood); levels of vitamins A, D, E and beta-carotene; prothrombin time; adverse events Setting and length of treatment 12 centres in the USA. 5 week run-in followed by 52 week DB treatment phase	Population Not stated Inclusion criteria For run-in Aged > 18 year; BMI 28-40 kg/m^2; type 2 diabetes maintained on oral sulfonylureas for the 6 months prior to the trial; stable plasma glucose on a second-generation sulfonylurea agent (glyburide or glypizide) as the only oral hypoglycaemic agent at trial entry For DB phase ≥70% adherence with drug regimen during run-in (assessed by counting capsules); HbA_{1c} of 6.5-10% at screening; fasting plasma glucose level of 5.6-12.2 mmol/l at the end of week 4 of run-in; blood levels of fat-soluble vitamins above the lower limit of reference range Exclusion criteria Pregnancy; lactation; women of childbearing potential not taking adequate contraceptive measures; clinically relevant condition that might affect study outcomes; significant complications associated with diabetes; weight loss >4 kg during the previous 3 months; hx of recurrent nephrolithiasis or symptomatic cholelithiasis, GI surgery for weight loss, hx of bulimia or laxative abuse; use of any drugs that might influence body weight or plasma lipids during the 8 weeks prior to trial	5 week, SB, placebo run-in period for all patients Nutritionally balanced, mildly hypocaloric diet containing 30% calories as fat, 50% as carbohydrate, and 20% as protein, with a maximum of 300 mg/day of cholesterol. Patients instructed in dietary requirements and in procedures for completing food intake records. All previous vitamin supplements were discontinued. Prescribed placebo and oral hypoglycaemic agent (glypizide or glyburide) at doses determined by patient's physician; constant dose maintained during the 2 weeks prior to randomisation. (n=391) Standard care for all patients during DB study Hypocaloric diet (energy deficit 500 kcal/day). Additional dietary counselling and supplements given to patients with 2 consecutive fat-soluble vitamin measurements below the reference range C: Placebo tid with meals for 52 weeks (n=159) I: Orlistat 120 mg tid with meals for 52 weeks (n=163)	Gender no. m/f C: 85/74 I: 79/83 Mean±sd age (years) C: 54.7±9.7 I: 55.4±8.8 Race no. White/Black/Hispanic/other C: 140/9/6/4 I: 141/13/4/4 Mean±sd weight (kg) C: 99.7±15.4 I: 99.6±14.5 Mean±sd BMI (kg/m^2) C: 34.0±3.4 I: 34.5±3.2 Fasting plasma glucose (mmol/l) C: 9.09±1.87 I: 8.85±1.68 HbA_{1c} (%) C: 8.2±1.07 I: 8.05±0.98	Statistical techniques ITT analysis included patients who had received at least one dose of study medication and a subsequent efficacy observation. Safety analysis included those who had received one dose of trial medication and a subsequent safety observation. ANOVA and ANCOVA to test null hypothesis. The placebo adjusted 95% CI of orlistat treatment effect (LSM) was determined. Mean±sem weight loss during run-in (kg) C: 2.24±0.14 I: 2.07±0.15 Mean±sem % weight loss from beginning of run-in to end of 57 weeks (ITT) C: 4.3±0.5% I: 6.2±0.5% LSM difference between treatment groups (2.4 kg) was significant (p<0.001) Mean±sem % weight loss from beginning of run-in to end of 57 weeks (completers) C: 4.2±0.5% I: 6.3±0.4% Mean±sem weight loss (kg) (ITT) C: 4.31±0.57 I: 6.19±0.51 P<0.001	Withdrawals during DB phase C: 44/159 (28%) 23 withdrawals due to A/Es I: 24/163 (15%) 12 withdrawals due to A/Es Completers C: 116/159 (73%) I: 139/163 (85%) Reasons for withdrawal Adverse events Loss to follow-up Non-adherence (n=4) Administrative Protocol violations Treatment failure Withdrawal due to raised plasma glucose levels on at least 3 occasions despite maximum sulfonylurea medication C: 15 patients (8.8%) I: 5 patients (2.5%) Experienced at least 1 GI A/E C: 59% I: 79% GI events usually occurred early during treatment, were mild to moderate in intensity, generally transient, and resolved spontaneously No. withdrawals due to GI A/Es C: 2 I: 7 There was no evidence for the development of gallstones or renal stones after orlistat treatment.	Limitations of the study, as noted by the study authors None stated Sponsorship Hoffman-La Roche

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
				<u>Loss of ≥5% of initial body weight</u> C: 22.6% I: 48.8% P<0.001 <u>Loss of ≥10% of initial body weight</u> C: 8.8% I: 17.9% P<0.017	Mean plasma levels of vitamins A, D, E and beta-carotene remained within the reference range throughout the study. After 52 weeks, mean vitamin E and beta-carotene levels were significantly lower in I vs C (p<0.001). However, there was no significant change in vitamin E-LDL ratio in either group. Vitamin D supplementation was required in C 7% and I 17%, vitamin E in 1% of both groups, and beta-carotene in I 9%. Prothrombin times did not differ between groups, and did not fall below the reference range.	

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
				Decrease in mean±sem fasting plasma glucose levels during run-in C: 1.16±0.13 mmol/l I: 0.98±0.13 mmol/l Additional change in mean±sem fasting plasma glucose levels from randomisation to end of study C: 0.54±0.15 mmol/l I: -0.02±0.14 mmol/l P<0.001 Values in subset of patients with fasting plasma glucose ≥7.77 mmol/l at start of DB phase C: +0.36±0.27 mmol/l I: -0.47±0.19 mmol/l P<0.001 Decrease in mean±sem fasting plasma insulin levels at 52 weeks C: 4.3±6.3% I: 5.2±4.4% n.s.		

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
				Mean HbA_{1c} levels during run-in, by around 7.5% in both groups Additional change in mean±sem HbA_{1c} levels from randomisation to end of study C: 0.18±0.11% I: -0.28±0.09% P<0.001 Values in subset of patients with HbA_{1c} levels >8% at start of DB phase C: -0.05±0.29% I: -0.53±0.18% P<0.001 Decreased/discontinued sulfonylureas C: 28.9% / 0 I: 43.2% / 11.7% Changes in lipid levels Decreases were similar in both groups during run-in. After randomisation, I patients demonstrated improved parameters vs C, with statistically significant differences for total cholesterol, LDL-C, LDL-HDL ratio (p<0.001 for both), triglycerides (p=0.036), and apolipoprotein B (p<0.001) Mean±sem change in waist circumference at 52 weeks C: -2.0±0.5 cm I: -4.8±0.5 cm P<0.01		

Abbreviations: tid – three times per day, DB – double blind, BMI – body mass index, hx – history, SB – single blind, C – control group, I –intervention group, no. – numbers, m – male, f – female, sd – standard deviation, LDL – low density lipoprotein, ANOVA – analysis of variance, ANCOVA – analysis of covariance, ITT – intention-to-treat analysis, sem – standard error of the mean, n.s. – not significant, HDL – high density lipoprotein, GI – gastrointestinal, A/E – adverse events, 95% CI – 95% confidence intervals, LSM – least squares mean.

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Finer et al (2000)[40] UK Aim To assess the efficacy and tolerability of orlistat in producing and maintaining weight loss over a 12 month period Method of randomisation Blinded code numbers, randomised in blocks of four, were printed on the labels of DB medication (matching orlistat and placebo) and supplied in identical blister packs to each study centre. Patients were randomised in blocks to give equal numbers of orlistat and placebo patients. Patients stratified according to weight lost during run-in (≤2.0 kg and >2.0 kg) Outcomes Change in body weight; waist circumference; adverse events; serum lipid levels; fasting serum insulin levels; fasting serum glucose levels; plasma levels of vitamins A, D, and E, and beta carotene; haematology; fasting blood chemistry; urinalysis; faecal occult blood; sitting BP; heart rate; adherence; adverse events Setting and length of treatment 5 centres in UK. 4 week run-in followed by 52 week DB treatment phase	Population Obese patients recruited by local advertisement or by referral from general practitioners Inclusion criteria For run-in Age at least 18 years; BMI 30-43 kg/m^2; women of childbearing potential who were taking adequate contraceptive measures; For DB phase >75% compliance with drug regimen (calculated from number of returned capsules) during run-in Exclusion criteria Weight loss >4 kg in the 3 months prior to screening; hx any serious disease, including diabetes; uncontrolled hypertension; previous GI surgery for weight reduction; hx of post-operative adhesions; hx or presence of cancer; psychiatric or neurological disorder requiring chronic mediation or liable to prejudice adherence; evidence of alcohol or substance abuse; bulimia or evidence of laxative abuse; pregnancy or lactation; post-menopausal women who had been amenorrhoeic for less than 1 year; taking drugs capable of influencing body weight, resins for lipid lowering, anti-coagulants, digoxin, or lipid-soluble vitamin supplements within the previous month	4 week, SB, placebo run-in period for all patients Nutritionally balanced low energy diet, providing 30% of energy from fat, designed to produce an individually tailored energy deficit of 600 kcal/day, to produce weight loss of 0.25-0.5 kg/week. The lowest prescribed energy intake was 1200 kcal/day. Alcohol consumption limited to 150g/week. Placebo tid with meals. (n=267) Standard care for all patients during 52 week DB study Dietary regimen as above until end of week 24, when prescribed daily energy intake reduced by 300 kcal/day in all patients, regardless of whether or not body weight had stabilised. Patients prescribed 1200 kcal/day at screening had energy intake adjusted to 1000 kcal/day at the end of week 24 and maintained to end of week 52. C: Placebo tid with meals (n=114) I: Orlistat 120 mg tid with meals (n=114)	Gender no. m/f C: 13/95 I: 12/98 Mean±sd age (years) C: 41.4±10.0 I: 41.5±10.5 Race no. white/black/other C: 104/1/3 I: 103/2/5 Mean±sd weight (kg) C: 98.4±15.0 I: 97.9±12.9 Mean±sd BMI (kg/m^2) C: 36.8±3.7 I: 36.8±3.6 Elevated LDL levels (≥3.36 mmol/l) C: 53% I: 52% Elevated SBP (≥140 mmHg) C: 2% I: 5.5% Elevated DBP (≥90 mmHg) C: 22% I: 18%	Statistical techniques ANOVA to test null hypothesis. For each centre, 95% CI of treatment difference based on least squares mean was provided and the least squares mean difference from each centre used to explore any centre by treatment interaction. The least squares mean was compared as the primary endpoint for analysis. ITT analysis included patients who were assessed clinically and received at least one dose of study medication; included observed data and data from the last observation carried forward to week 52. Completer analysis included patients who completed 52 weeks of treatment without protocol violation. Average weight loss (ITT) at 52 weeks C: 5.4% I: 8.5% P=0.016 Average weight loss (completers) at 52 weeks C: 5.5% I: 8.8% n.s. At 24 weeks The LSM difference from placebo for change in body weight was 1.8 kg (95% CI: -2.96, -0.56; p=0.004) for orlistat-treated patients in the ITT population. For completers, the values were 2.4 kg (95% CI: -3.82, -0.88; p=0.002)	During run-in Lost to F/U 18 Uncooperative 7 A/E 5 Entry violation 5 Administrative 2 Protocol viol 1 Refused rx 1 Total 39/267 (15%) During 52 week DB study C/I Lost to F/U 18/15 Uncooperative 8/7 A/E 7/9 Administrative 5/3 Protocol viol 3/5 Refused rx 5/2 Rx failure 2/0 Total 48/41 ITT analysis 10 patients were excluded from the ITT analysis, 6 due to insufficient safety assessments, and 4 due to insufficient evaluations for efficacy, leaving C: 108 I: 110 Completed treatment C: 66 I: 73 Completer analysis C: 61 I: 59 Adverse events 82.1% patients in I versus 56.4% in C had at least one GI event. 59% in I and 15.4% in C patients had at least one of the following events: loose stools, increased defecation, abdominal pain, uncontrolled oily discharge, faecal urgency, nausea/vomiting, discoloured faeces, flatulence, decreased defecation. Most events occurred early in the study and were generally transient (≤4 days)	Limitations of the study, as noted by the study authors Larger and longer trials are necessary to adequately evaluate adverse effects such as gallstone and renal stone formation in association with the use of orlistat Patients prescribed orlistat may require supplementation of fat soluble vitamins, as more patients with low or marginal vitamin levels may be met in clinical practice (as opposed to in trials) Sponsorship Hoffmann-La Roche

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
				At 52 weeks The LSM difference from placebo for change in body weight was 2.0 kg (95% CI: -3.6, -0.38; p<0.05) for orlistat-treated patients in the ITT population. For completers, the values were 2.5 kg (95% CI: -5.38, 0.42; p=0.092) When ITT data were stratified by weight loss during run-in, those losing >2 kg during run-in lost more weight at 52 weeks with orlistat than those losing ≤2.0 kg during run-in. Patients losing more than 10% of initial body weight (including run-in) (ITT) C: 17% I: 28% P=0.04 Patients losing more than 10% of initial body weight (during DB treatment) (ITT) C: 6% I: 16% P=0.02 Patients losing more than 5% of initial body weight (during DB treatment) (ITT) C: 21% I: 35% P=0.02	3 patients in I withdrew due to GI adverse events (abdominal pain, liquid stools, increased defecation) and 1 patient in C withdrew due to oesophagitis Other reported adverse events included upper respiratory tract infection (I: 6.3% C: 5.4%), pharyngitis (I: 6.3% C: 2.7%), influenza (I: 12.5% C: 10.0%), headache (I: 10.9% C: 8.9%), and back pain (I: 4.5% C: 2.7%) Vitamin A, D, and E supplementation was given to 1.8%, 8.0%, and 3.6% respectively of I patients, compared with 0.9% of C patients for each vitamin type. During the study 7% of I and 11% of C patients developed gallbladder abnormalities, and 3% and 2% respectively developed renal abnormalities.	

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
				Mean decrease in waist circumference at 52 weeks in females with measurement ≥88 cm at baseline C: 5.1 cm I: 6.3 cm n.s. Mean decrease in waist circumference at 52 weeks in males with measurement ≥102 cm at baseline C: 3.9 cm I: 4.1 cm n.s. Weight regain between 24 and 52 weeks C: 1.34% patients regained I: 0.6% patients regained Lipid levels Orlistat-treated patients showed significant decreases ($p<0.05$) in serum levels of total cholesterol, and LDL, and in the LDL-HDL ratio in comparison with placebo. There were no significant between group differences for triglycerides, lipoprotein (a), and VLDL. HDL levels increased by similar amounts in both groups. In patients with elevated LDL (≥3.36 mmol/l) at the start of DB treatment, the mean value decreased after 52 weeks by C: 1.3% and I: 7.1% There was a trend towards a reduction in fasting insulin, and, to a lesser extent, in fasting glucose levels associated with weight loss in both groups. Between weeks 24 and 52, DBP tended to fall in patients with elevated levels (≥90 mm Hg) at baseline		

Abbreviations: DB – double blind, BP – blood pressure, BMI – body mass index, hx – history, GI – gastrointestinal, SB – single blind, tid – three times per day, C – control group, I –intervention group, no. – numbers, m – male, f – female, sd – standard deviation, LDL – low density lipoprotein, SBP – systolic blood pressure, DBP diastolic blood pressure, ANOVA – analysis of variance, 95% CI – 95% confidence intervals, ITT – intention-to-treat analysis, n.s. – not significant, LSM – least squares mean, HDL – high density lipoprotein, VLDL – very low density lipoprotein, F/U – follow-up, A/E – adverse events, viol – violation, rx – treatment.

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Davidson et al (1999)[41] USA Aim (1) To test the hypothesis that orlistat combined with dietary intervention is more effective than placebo for weight loss and maintenance over 2 years. (2) To examine the effectiveness of 2-year orlistat administration in improving blood pressure, lipid, and carbohydrate metabolism abnormalities. Method of randomisation The method of randomisation was not stated. Randomisation was conducted in 2 stages. First stage: year 1 (weight loss). Second stage: year 2 (weight maintenance). Participants were stratified at year 1 randomisation according to whether >2 kg or <2 kg lost during run-in. Outcomes Change in body weight; standing waist circumference; BP; levels of vitamins A, D, E, and beta carotene; prothrombin time; fasting serum glucose and insulin levels; glucose tolerance; lipid levels; adverse effects Setting and length of treatment 18 clinical research centres in the USA. 2 year study	Population Not stated Inclusion criteria For run-in phase Age >18 years; BMI 30-43 kg/m^2; adequate contraception in women of childbearing potential; no weight loss (>4 kg) in previous 3 months. For year 1 (weight loss) Participants with a treatment adherence of at least 75% (assessed by counting placebo capsules taken during run-in) were randomised to receive placebo or orlistat 120 mg For year 2 (weight maintenance) Participants who completed first year of treatment, with a treatment adherence of at least 70% entered maintenance phase. Participants treated with orlistat during year 1 were randomised to receive placebo, orlistat 60 mg, or orlistat 120 mg. Participants taking placebo during year 1 continued to take placebo during year 2.	4-week, SB, placebo run-in period for all patients Controlled energy diet providing 30% of energy intake as fat. Energy intake was prescribed for each participant on the basis of estimated daily maintenance energy requirement. All vitamin and mineral preparations were discontinued 8 weeks prior to beginning the study (n=1187) Weight loss phase (DB) Standard care for all patients Controlled energy diet continued (as above); 4 behaviour modification sessions on weight loss strategies. Dieticians provided instruction on dietary intake recording, and later used participants' food diaries for counselling. Participants encouraged to walk briskly for 20-30 minutes 3-5 times per week. C1: Placebo, tid with meals, for 52 weeks (n=224) (ITT n=223) I1: Orlistat 120 mg, tid with meals, for 52 weeks (n=668) (ITT n=657)	Gender no. m/f C1: 26/197 I1: 113/544 Age mean±sd years C1: 44.0±0.7 I1: 43.3±0.6 Race % white/black/hispanic C1: 79.4/15.7/4.0 I1: 81.3/13.4/4.3 Weight mean±sd (kg) C1: 100.6±0.9 kg I1: 100.7±0.6 kg BMI mean±sd (kg/m^2) C1: 36.5±0.9 I1: 36.2±0.1 Abnormal oral glucose tolerance test results Impaired/diabetic C1: 5.8% / 4.5% I1: 6.1% / 4.0% Abnormal fasting insulin level C1: 30.5% I1: 36.7% Abnormal LDL level C1: 35.9% I1: 32.1% Abnormal HDL level C1: 12.1% I1: 15.2% Abnormal triglycerides level C1: 5.4% I1: 10.5%	Statistical techniques ITT analysis using last value carried forward included those receiving at least 1 dose of medication during DB treatment, with at least 1 body weight measurement before and after randomisation. ANOVA and ANCOVA used to assess between group differences in mean change in body weight and to compare weight change in year 1 with that in year 2. ANCOVA used to evaluate changes in risk factors, using baseline values as covariates. Overall weight loss during run-in Approx 2.3 kg (2.3% of initial body weight) Results at end of year 1 Mean±sem weight loss C1: 5.81±0.67 kg I1: 8.76±0.37 kg P<0.001 Mean±sem % weight loss C1: 5.8%±0.7% I1: 8.8%±0.4% P<0.001 Loss of >5% initial weight C1: 43.6% I1: 65.7% P<0.01 Loss of >10% initial weight C1: 24.8% I1: 38.9% P<0.004	During 4-week run-in no. (%) Lost to F/U 43 (3.6%) Admin 53 (4.5%) A/E 23 (1.9%) Uncooperative 64 (5.4%) Rx failure 0 Protocol viol 12 (1.0%) Entry viol 98 (8.3%) Refused rx 1 (0.1%) Total withdrawn 24.8% During year 1 Lost to F/U C1: 21 (9.4%) I1: 59 (8.8%) Admin C1: 21 (9.4%) I1: 42 (6.3%) A/E C1: 9 (4.0%) I1: 61 (9.1%) Uncooperative C1: 16 (7.1%) I1: 26 (3.9%) Rx failure C1: 11 (4.9%) I1: 6 (0.9%) Protocol viol C1: 5 (2.2%) I1: 13 (1.9%) Entry viol C1: 1 (0.4%) I1: 3 (0.4%) Refused rx C1: 2 (0.9%) I1: 0 Total withdrawn C1: 38.3% I1: 31.3%)	Limitations of the study, as noted by study authors (1) High withdrawal rate (2) Potential bias due to lack of treatment efficacy in the placebo group and GI events in the orlistat group. This could have caused unplanned unblinding. The possible biases are such that, the effectiveness of orlistat could be underestimated or overestimated. However, application of the last observation carried-forward approach to the ITT population should minimise the opposing sources of bias. Reviewer's comments Most results are based on comparisons between those receiving placebo for 2 years and those receiving orlistat 120 mg for 2 year, and other treatment combinations are not taken into account. The analysis of mean±sem body weight change during the two years (presented as a figure in the paper) is based on the groupings for year 2, and the year 1 comparison between placebo and orlistat 120 mg is not shown Sponsorship Hoffman-La Roche

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
	Exclusion criteria Frequent change of smoking habits; smoking cessation within last 6 months; history or presence of substance abuse; excessive alcohol intake; significant cardiac, renal, hepatic, gastrointestinal, psychiatric, or endocrine disorder; drug-treated type-2 diabetes mellitus; concomitant use of medications that alter appetite or lipid levels.	Maintenance phase Standard care for all patients Weight maintenance diet; 4 seminars on weight-maintenance strategies. C2: Participants receiving placebo in weight loss phase: placebo, tid with meals, for 52 weeks (n=133) C3: Participants receiving orlistat 120 mg in weight loss phase: placebo, tid with meals, for 52 weeks (n=138) I2: Participants receiving orlistat 120 mg in weight loss phase: orlistat 60 mg, tid with meals, for 52 weeks (n=152) I3: Participants receiving orlistat 120 mg in weight loss phase: orlistat 120 mg, tid with meals, for 52 weeks (n=153)	Diastolic BP >90 mm Hg Untreated/treated C1: 7.2% / 1.8% I1: 5.5% / 2.7%	Results at end of year 2 Mean±sem (%) weight regain C3: 5.63±0.42 kg (63.4%) 12: 4.26±0.57 kg (51.3%) I3: 3.2±0.45 kg (35.2%) P<0.001 C3 vs I3 and I2 vs I3 Mean±sem % weight loss C2: 4.5%±0.9% C3: 4.2%±0.8% I3: 7.6%±0.9% % participants maintaining >10% loss C2: 17.5% I3: 34.1% P=0.02 Change in SBP at 1 year mean±sem mm Hg C1: change from 118.6±0.9 to 119.6±1.3 I1: change from 119.4±0.5 to 118.6±0.6 P=0.002 Change in DBP at 1 year mean±sem mm Hg C1: change from 76.1±0.6 to 77.4±0.9 I1: change from 76.9±0.4 75.9±0.4 P=0.009 Decrease in waist circumference mean±sem cm at 2 years Placebo –2.38±1.0 Orlistat –4.52±0.8 P<0.05 NB unclear exactly which groups these are	During year 2 Lost to F/U C2: 15 (11.3%) C3: 15 (10.9%) I2: 22 (14.5%) I3: 17 (11.1%) Admin C2: 2 (1.5%) C3: 6 (4.3%) I2: 2 (1.3%) I3: 8 (5.2%) A/E C2: 4 (3.0%) C3: 6 (4.3%) I2: 9 (5.9%) I3: 5 (3.3%) Uncooperative C2: 5 (3.8%) C3: 4 (2.9%) I2: 6 (3.9%) I3: 6 (3.9%) Rx failure C2: 3 (2.3%) C3: 6 (4.3%) I2: 4 (2.6%) I3: 3 (2.0%) Protocol viol C2: 3 (2.3%) C3: 6 (4.3%) I2: 5 (3.3%) I3: 3 (2.0%) Entry viol C2: 0 C3: 0 I2: 0 I3: 0 Refused rx C2: 3 (2.3%) C3: 0 I2: 2 (1.3%) I3: 2 (1.3%) Total withdrawn C2: 26.5% C3: 31.0% I2: 32.8% I3: 28.8% Completion rates at end of year 2 not significantly different between treatment groups Adverse events At least 1 GI event C2: 59% I3: 79% Most GI events occurred early during treatment, were mild to moderate in intensity, and resolved spontaneously.	

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
				Total cholesterol levels at 2 years mean ±sem mmol/L C2: 5.19±0.10 I3: 5.04±0.09 P<0.001 LDL levels at 2 years mean ±sem mmol/L C2: 3.22±0.09 I3: 3.14±0.08 P<0.001 HDL levels at 2 years mean ±sem mmol/L C2: 1.36±0.04 I3: 1.28±0.03 P=0.11 Triglyceride levels at 2 years mean ±sem mmol/L C2: 1.56±0.16 I3: 1.51±0.08 P=0.64 Changes in lipid levels were independent of weight loss Increase in fasting serum glucose over 2 years C2: from 5.60±0.03 to 5.80±0.06 mmol/L I3: from 5.62±0.03 to 5.67±0.05 mmol/L P=0.001 Decrease in fasting serum insulin over 2 years C2: from 86.37±4.71 to 86.32±6.89 pmol/L I3: from 84.02±3.46 to 66.52±3.92 pmol/L P=0.04 Decrease in insulin levels appeared to be related to weight loss, rather than an independent drug effect	There were no apparent systematic differences in weight loss among participants who experienced several, one, or no GI adverse effects Withdrawals due to GI events C2: 2 participants I3: 7 participants The A/E rate was lower in year 2 than in year 1 and did not differ significantly between groups Requirement for supplemental fat-soluble vitamins or beta-carotene C2: 6.5% I3: 14.1% Levels of vitamin D and vitamin E decreased in I in year 1 (p=0.001 and p=0.03 respectively) but remained within the reference range Dx of breast cancer during the 2 year study C2: 1 participant (identified prior to starting study) I3: 3 participants (1 identified prior to starting study, 1 identified 32 days after randomisation)	

Abbreviations: BMI – body mass index, SB – single blind, DB – double blind, tid – three times per day, ITT – intention-to-treat analysis, no. – number, m – male, f – female, sd – standard deviation, LDL – low density lipoprotein, HDL – high density lipoprotein, BP – blood pressure, ANOVA – analysis of variance, ANCOVA – analysis of covariance, sem – standard error of the mean, SBP – systolic blood pressure, DBP – diastolic blood pressure, F/U – follow-up, admin – administrative, A/E – adverse events, rx – treatment, viol – violation, GI – gastrointestinal, dx – diagnosis, C1 – first control group, C2 – second control group, C3 – third control group, I1 – first intervention group, I2 – second intervention group, I3 – third intervention group.

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Hauptman et al (2000)[42] USA Aim To evaluate the long-term efficacy and tolerability within primary care settings of orlistat for the treatment of obesity Method of randomisation Not stated Outcomes Change in body weight; waist circumference; serum lipid levels; fasting serum glucose and insulin levels; BP; adverse events; haematology; blood chemistry including levels of vitamins A, D, E, and beta-carotene; prothrombin time; urinalysis; 24 hour urine test; faecal occult blood Setting and length of treatment 17 primary care centres in the USA. 4 week run-in. 52 week DB weight loss phase, then 52 week DB maintenance phase.	Population Not stated Inclusion criteria For run-in Age >18 years; BMI 30-44 kg/m^2 For DB phase ≥75% adherence with drug regimen during run-in (assessed by counting returned capsules) Exclusion criteria Pregnancy; lactation; women of childbearing potential not taking adequate contraceptive measures; weight loss of >4 kg during the 3 months prior to the study; hx of significant cardiac, renal, hepatic or GI disorders; uncontrolled hypertension or any other clinically significant condition; GI surgery for weight reduction; bulimia or laxative and/or substance abuse; abnormal laboratory measures; changes in smoking habits in the 6 months prior to the study; use of any drug that might influence body weight or food intake during the 8 weeks prior to screening.	4 week, SB, placebo run-in period for all patients Nutritionally balanced reduced energy diet, providing 30% energy as fat, 50% as carbohydrate, 20% as protein, and containing 300 mg/day cholesterol maximum. Alcohol consumption limited to maximum of 10 drinks per week. The prescribed energy intake was 5020 kJ/day for patients who weighed less than 90 kg initially and 6275 kJ/day for those who weighed 90 kg or more initially. Dietary guidance provided by study physician. Placebo tid. (n=796) Standard care for all patients during DB study Year 1: dietary regimen as above for 52 weeks. Videos on behaviour modification techniques showed at 4 points. Year 2: weight maintenance diet for further 52 weeks: prescribed energy intake increased by 1255 kJ/day for those who were still losing weight at 52 weeks. No dietary adjustment was made for those whose weight remained stable. Patients given weight management and diet leaflets designed to assist with weight maintenance at 4 points. Patients completed 3-day diet diaries at 10 points during the study, having received instructions from staff and viewed a video on food records. Patients were encouraged to walk briskly for 20-30 minutes 3-5 time per week.	Characteristics of patients randomised at the beginning of year 1 Gender no. m/f C: 47/165 I1: 47/166 I2: 44/166 Mean±sem age (years) C: 41.6±0.7 I1: 42.6±0.8 I2: 43.2±0.7 Race no. white/black/American Indian/Hispanic/other C: 193/15/0/4/0 I1: 200/9/0/2/2 I2: 184/19/1/6/0 Mean±sem weight (kg) C: 101.8±1.00 I1: 100.4±1.00 I2: 100.5±0.98 Mean±sem BMI (kg/m^2) C: 36.1±0.3 I1: 35.8±0.3 I2: 36.0±0.2	Statistical techniques ITT analyses included patients who had received at least 1 dose of DB medication, and had at least 1 follow-up body weight measurement. ANOVA and ANCOVA used to assess group differences in changes in body weight. The 95% CI of treatment difference based on the LSM was also determined. LOCF technique was used for 1- and 2-year analyses, using observed actual values rather than derived data. Chi-square used to analyse differences in proportions. Mean±sem weight change (kg) at 1 year (ITT) C: -4.14±0.56 I1: -7.08±0.54 I2: -7.94±0.57 P=0.001 C vs I1 and C vs I2 Mean±sem weight change (kg) at 1 year (completers) C: -4.26±0.58 I1: -7.92±0.70 I2: -8.78±0.73 P=0.001 C vs I1 and C vs I2 Mean±sem weight change (kg) at 2 years (ITT) C: -1.65±0.62 I1: -4.46±0.61 I2: -5.02±0.73 P=0.001 C vs I1 and C vs I2	Withdrawals during run-in 161/796 (20%) withdrew Withdrawals during year 1 (weight loss phase) C: 90/212 (42%) I1: 59/213 (28%) I2: 59/210 (29%) Withdrawals during year 2 (weight maintenance phase) C: 31/122 (25%) I1: 34/154 (22%) I2: 34/151 (23%) Reasons for withdrawal during 2-year DB phase (%) C/I1/I2 Lost to F/U 16.5/13.1/15.2 Admin 17.5/7.5/6.7 A/E 7.1/6.6/11.0 Uncoop 5.2/5.2/4.3 Protocol viol 3.8/5.2/4.3 Rx failure 3.8/3.3/1.9 Refused rx 3.3/2.8/0.5 Died 0/0/0.5 (1 pt) The patient died of acute MI after 301 days of treatment Rates of withdrawal due to A/Es did not differ significantly between groups Total no. (%) withdrawals during 2-year DB phase C: 121 (57.1%) I1: 94 (46.2%) I2: 97 (46.2) P<0.05 C vs I1 and C vs I2 Completers at end of year 2 C: 91 I1: 120 I2: 117	Limitations of the study, as noted by the study authors One aspect of the study does not relate to actual clinical practice: if patients started to regain weight in year 2, they were instructed not to resume a reduced-energy diet, but rather avoid further weight gain. Under realistic clinical practice conditions, patients who relapsed would most likely be encouraged to reduce their energy intake for a period to reverse the weight gain. Sponsorship Not stated, but first author is based at Hoffman-La Roche, Nutley, NJ, USA.

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
		C: Placebo tid with main meals for 104 weeks (n=212) I1: Orlistat 60 mg tid for 104 weeks (n=213) I2: Orlistat 120 mg tid for 104 weeks (n=210)		Mean±sem weight change (kg) at 2 years (completers) C: -1.54±0.58 I1: -4.58±0.68 I2: -5.16±0.78 P=0.02 C vs I1, p=0.002 C vs I2 % losing at least 5% of initial weight at 1 year (ITT) C: 30.7% I1: 48.8% I2: 50.5% P<0.001 C vs I1 and C vs I2 % losing at least 10% of initial body weight at 1 year (ITT) C: 11.3% I1: 24.4% I2: 28.6% P<0.001 C vs I1 and C vs I2 % maintaining at least 5% of initial weight loss at 2 years (ITT) C: 24.1% I1: 33.8% I2: 34.3% P<0.03 C vs I1, p<0.02 C vs I2 % maintaining at least 10% of initial weight loss at 2 years (ITT) C: 6.6% I1: 14.6% I2: 18.6% P=0.008 C vs I1, p<0.001 C vs I2	Adverse events % patients reporting GI events over 2 years C: 59% I1: 72% I2: 79% P=0.003 C vs I1, p=0.001 C vs I2 Specific GI events (faecal urgency, oily spotting, oily stool, flatus with discharge, oily evacuation, increased defecation, faecal incontinence) occurred more frequently in I1 and I2 vs C (p=0.001). Most GI events were mild to moderate in intensity, were limited to only 1 or 2 episodes per patient, and occurred early during treatment. Few GI events were reported during year 2. No. (%) withdrawal due to GI events C: 3 (1.4%) I1: 10 (4.7%) I2: 12 (5.7%) Fat soluble vitamins Vitamins A, D and E and beta-carotene levels remained within reference ranges in all groups during 2 years. 2 consecutive low vitamin E and beta-carotene values occurred sig more frequently in patients treated with orlistat vs placebo. The frequency of 2 consecutive low level vitamin A and D values did not significantly differ between groups. Beta-carotene supplementation was required by 2.4% in C, 4.3% in I1 and 6.3% in I2.	

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
				% (kg) of initial weight lost at 2 years C: 1.70±0.62 (1.65±0.62) I1: 4.44±0.61 (4.46±0.61) I2: 5.01±0.79 (5.02±0.73) P<0.001 C vs I1 and C vs I2 Weight regain at year 2, expressed as % lost in year 1 C: 60% I1: 37% I2: 38% Cardiovascular risk factors At 1 year, total cholesterol and LDL levels were significantly lower in I1 and I2 vs C (p=0.001), and this was generally maintained during year 2. Differences between groups for triglycerides and glucose levels n.s. at all times. Fasting insulin levels in I2 lower than C at 1 year (p<0.05). DBP decreased in I1 at 1 year (-0.97±0.01 mm Hg; p=0.02). Changes in C and I2 n.s. During year 2 no significant changes between groups for DBP, but SBP in I2 reduced (p=0.04) vs C. Similar pattern of results for ITT and completers.		

Abbreviations: tid – three times per day, DB – double blind, BMI – body mass index, hx – history, SB – single blind, C – control group, I1 – first intervention group, I2 – second intervention group, no. – numbers, m – male, f – female, sd – standard deviation, LDL – low density lipoprotein, ANOVA – analysis of variance, ANCOVA – analysis of covariance, ITT – intention-to-treat analysis, sem – standard error of the mean, n.s. – not significant, vs – versus, GI – gastrointestinal, A/E – adverse events, BP – blood pressure, 95% CI – 95% confidence intervals, LSM – least squares mean, LOCF – last observation carried forward, F/U – follow-up, admin – administrative, uncoop – did not co-operate, viol – violation, rx – treatment, MI – myocardial infarction.

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Sjostrom et al (1998)[43] Sweden, Finland, Denmark, Switzerland, Netherlands, France Aim To assess the efficacy and tolerability of orlistat in producing and maintaining weight loss; to assess effects on cardiovascular risk factors Method of randomisation Random number codes. Randomisation in blocks of 4, (investigators blind), to give equal numbers of patients in both groups. Patients stratified according to weight loss during run-in (≤2 kg or >2 kg). Patients were reassigned at the end of year 1 for the weight maintenance phase. Outcomes Change in body weight; fasting serum levels of glucose, insulin and lipids; haematology, clinical chemistry (including vitamins A, D, and E levels), prothrombin time, beta-carotene levels, and urinalysis; plasma orlistat levels; adverse events Setting and length of treatment 15 European centres. 4 week run-in, then 52 week DB weight loss phase, followed by further 52 weeks DB weight maintenance phase	Population Obese patients recruited from hospital waiting lists or by local advertising. Inclusion criteria For run-in Age ≥18 years; BMI 28-47 kg/m^2, women of childbearing potential using adequate contraception For DB phase (year 1 weight loss) >75% adherence with run-in regimen, assessed by counting number of returned placebo capsules For DB phase (year 2 weight maintenance) >75% adherence with regimen Exclusion criteria Serious disease including uncontrolled hypertension and pharmacologically treated diabetes; weight loss of >4 kg in the 3 months prior to screening; prior surgery for weight reduction; hx of post-operative adhesions; bulimia or laxative abuse; use of drugs that could influence body weight or lipid levels in the month prior to study entry; drug or alcohol abuse	4 week, SB, placebo run-in period for all patients Reduced energy diet containing 30% energy as fat (minimum prescribed energy intake was 1200 kcal/day, energy deficit 600 kcal/day). Energy content of diet calculated from patients' estimated basal metabolic rate, multiplied by 1.3 to estimate the total daily energy expenditure. Placebo tid with meals. (n=743) Standard care for all patients during DB study (year 1) Dietary regimen as above up to week 24 when prescribed energy intake was reduced by 300 kcal/day. For patients initially prescribed the minimum energy intake, energy intake was adjusted to 1000 kcal/day. If 2 consecutive measurements of plasma levels of fat soluble vitamins were recorded, additional dietary counselling, or vitamin supplementation was provided.	Gender no. m/f C1: 57/283 I1: 59/284 Mean(range) age (years) C1: 44.3 (18.0-77.0) I1: 45.2 (20.0-76.0) Mean (range) weight (kg) C1: 99.8 (64.2-137.2) I1: 99.1 (61.0-148.6) Mean (range) BMI (kg/m^2) C1: 36.1 (29.2-43.5) I1: 36.0 (28.3-47.2) Waist circumference C1: 105.9 (71-135) I1: 105.4 (70-149) Cardiovascular risk factors Baseline values did not differ between groups	Statistical techniques ITT analyses included patients who had received at least 1 dose of test medication and at least 1 follow-up body measurement. For withdrawals the last available examination was carried forward to the end of year 1 or 2, in the LSM calculations. Null hypothesis tested with general linear models. ANCOVA used to assess year 1 weight loss with the following variables: treatment, centre, and weight loss stratum after run-in. During year 2 analyses, weight change from the start of the run-in to the end of year 1 was used as a covariate. Mean (%) decrease from start of run-in to end of year 1 C1: 6.1 kg (6.1%) I1: 10.3 kg (10.2%) Thus the decrease in weight was 68% greater in I1 than in C1 (LSM weight-loss difference from randomisation 3.9 kg, p<0.001) % patients losing more than 20% initial body weight at end of year 1 C1: 2.1% I1: 9.3% % patients losing 10.1-20.0% initial body weight at end of year 1 C1: 15.6% I1: 29.5% % patients losing 5.1-10.0% initial body weight at end of year 1 C1: 31.5% I1: 29.7%	5 early withdrawals (4 had no safety assessment, 1 received no trial medication) reduced the year 1 ITT population from 688 to 683 patients, of whom 544 completed treatment. At the end of year 1, 18 patients withdrew mainly due to non-adherence, and 253 patients from C1 and 273 patients from I1 were reassigned for year 2. At the end of year 2, the ITT population consisted of 519 (75% of randomised) patients of whom 435 (63% of randomised) completed treatment. Analysis of patients completing year 2 gave similar results to the ITT analysis. Adverse events (year 1) GI A/Es C1: 2/343 (0.6%) I1: 12/345 (3.5%) Other A/Es C1: 7/343 (2.0%) I1: 11/345 (3.2%) Other reasons C1: 74/343 (21.6%) I1: 38/345 (11.0%) Adverse events (year 2) GI A/Es C2: 2/126 (1.6%) C3: 0 I2: 5/127 (3.9%) I3: 2/135 (1.5%)	Limitations of the study, as noted by the study authors Study sample considered to be representative of individuals who seek help for their obesity. Sponsorship Hoffman-La Roche

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
		C1: Placebo tid with meals for 52 weeks (n=340) I1: Orlistat 120 mg tid with meals for 52 weeks (n=343) <u>Standard care for all patients during DB study (year 2)</u> Weight maintenance diet; pts advised not to use hypocaloric diet <u>Year 2 (maintenance)</u> C2: Received placebo during year 1. Now placebo tid with meals for 52 weeks (n=123) C3: Received orlistat during year 1. Now placebo tid with meals for 52 weeks (n=138) I2: Received placebo during year 1. Now orlistat 120 mg tid with meals for 52 weeks (n=125) I3: Received orlistat during year 1. Now orlistat 120 mg tid with meals for 52 weeks (n=133)		<u>% patients losing 0.1-5.0% initial body weight at year 1</u> C1: 32.7% I1: 23.6% <u>% patients with unchanged or increased body weight at year 1</u> C1: 18.2% I1: 7.9% <u>Effect of orlistat during year 2</u> I2: LSM difference in weight loss vs C3 3.6 kg (se 0.6) ($p<0.001$) I3: LSM difference in weight loss vs C3 2.4 kg (se 0.6) ($p<0.001$) At 2 years, 57.1% of patients in I3 maintained a weight loss greater than 5%. The figure for C2 was 37.4%	<u>Other A/Es</u> C2: 1/126 (0.8%) C3: 4/138 (2.9%) I2: 1/127 (0.8%) I3: 1/135 (0.7%) <u>Other reasons</u> C2: 21/126 (16.7%) C3: 17/138 (12.3%) I2: 19/127 (15.0%) I3: 18/135 (13.3%) Year 1: serious A/Es reported by 24 patients in C1 and 25 in I1, with 1 A/E in each group possibly related to treatment. Year 2: 2 serious A/Es occurred that were judged possibly related to treatment <u>No. of withdrawals in year 1</u> CI: 83 I1: 61 <u>No. of withdrawals in year 2</u> CI: 45 I1: 46	

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
				Cardiovascular risk factors I1 and I3 had significantly greater reductions in total cholesterol, LDL cholesterol, LDL-HDL ratio, glucose, and insulin, vs. C1 and C2 respectively, at 1 and 2 years respectively. There were significantly greater reductions in SBP and DBP at 1 year in I1 vs C1. Linear modelling showed that baseline risk-factor value and weight reduction were significant variables at 1 and 2 year for observed risk-factor changes. Treatment was also a significant predictor for change in total cholesterol at 1 year (p=0.0001) and at 2 years (p=0.0002), and for change in LDL cholesterol at 1 year (p=0.0003) and at 2 years (p=0.0463). At 2 years, treatment was also a significant predictor (p=0.0236) for change in LDL-HDL ratio	There were no clinically or statistically significant changes in the mean values of any laboratory measurements during the study, and the frequency of laboratory abnormalities was evenly distributed between groups Year 1: 41 in I1 and 18 in C1 had 2 or more consecutive low vitamin concentrations recorded but only 16 and 4 patients respectively received supplements. Year 2: supplementation received by 4 patients in I3, 1 in C2, 3 in I2, and 1 in C3. Pharmacokinetic analysis of blood samples showed minute concentrations of unchanged orlistat in the plasma of a few patients at 24 weeks, 52 weeks, and 104 weeks, indicating low systemic absorption of orlistat after 2 years of treatment.	

Abbreviations: tid – three times per day, DB – double blind, BMI – body mass index, hx – history, SB – single blind, C1 – first control group, C2 – second control group, C3 – third control group, I1 – first intervention group, I2 – second intervention group, I3 – third intervention group, no. – numbers, m – male, f – female, LDL – low density lipoprotein, HDL – high density lipoprotein, ANCOVA – analysis of covariance, ITT – intention-to-treat analysis, se – standard error of the mean, GI – gastrointestinal, A/E – adverse events, LSM – least squares mean, SBP – systolic blood pressure, DBP – diastolic blood pressure.

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Rossner et al (2000)[47] Sweden/Germany/The Netherlands/Switzerland Aim To determine the effect of orlistat on long-term weight loss, weight maintenance, and obesity-related risk factors Method of randomisation Not stated. Patients were stratified according to weight loss during run-in; however, the exact parameters of the stratification were not explained Outcomes Change in body weight; waist and hip circumferences; lipid levels; ECG; blood pressure; fasting blood glucose and insulin; quality of life (assessed by a 55-item, self-administered questionnaire)[53]; food intake (assessed with diaries); adverse events; serum levels of fat-soluble vitamins and beta-carotene. Setting and length of treatment 14 European centres. 2 year study (1 year weight loss followed by 1 year weight maintenance)	Population Not stated Inclusion criteria For run-in Age at least 18 years; BMI 28-43 kg/m^2; women of childbearing potential were eligible if using adequate contraception. For DB phase Completion of run-in period; at least 75% adherence with treatment (assessed by counting capsules) Exclusion criteria Pregnancy; lactation; any clinically significant condition that might affect the outcome of the study; weight loss of more than 4 kg during the previous 3 months; smoking cessation within previous 6 months; previous GI surgery for weight reduction; hx of post-operative adhesions; hx of bulimia or laxative abuse; use of any drug that might influence body weight or serum lipids during the 8 weeks before screening; uncontrolled hypertension; drug-treated diabetes mellitus; hx of symptomatic cholelithiasis.	4 week, SB, placebo run-in period for all patients Nutritionally balanced diet containing 30% of calories as fat, with 600 kcal/day energy deficit, plus placebo tid. All vitamin supplements were discontinued. (n=783) Standard care for all patients during DB study Diet as above for one year. Year 2 - diet as above with the following adjustment for those losing at least 3 kg between weeks 40 and 52: the daily energy intake was prescribed at a level equivalent to the estimated total daily energy expenditure minus 10% kcal/day. For those with vitamin or beta-carotene levels below the reference range for 2 consecutive measurements, supplemental vitamins were given. Fewer clinic visits during year 2. C: Placebo tid with main meals for 2 years (n=243) I1: Orlistat 60 mg tid with main meals for 2 years (n=242) I2: Orlistat 120 mg tid with main meals for 2 years (n=244)	Gender no. m/f C: 31/206 I1: 56/183 I2: 40/202 Mean±sd age (years) C: 44.3±10.8 I1: 44.7±10.7 I2: 43.6±11.4 Mean±sd weight (kg) C: 97.7±14.6 I1: 99.1±14.3 I2: 96.7±13.8 Mean±sd BMI (kg/m^2) C: 35.3±4.1 I1: 35.2±3.9 I2: 34.7±3.7 LDL-C ≥3.362 mmol/L (treated or untreated) C: 127/237 (54%) I1: 131/239 (55%) I2: 125/242 (52%) LDL-C <3.362 mmol/L (treated) C: 1/237 (0.4%) I1: 2/239 (0.8%) I2: 0/242 (0%) HDL-C <0.905 mmol/L C: 45/237 (19%) I1: 76/239 (32%) I2: 65/242 (27%) Triglycerides ≥2.54 mmol/L C: 24/237 (10%) I1: 30/239 (13%) I2: 20/242 (8%)	Statistical techniques The 'safety' analysis included those who had received one dose of trial medication after randomisation and had a subsequent safety observation. The ITT analyses were based on LOCF and included participants who had received at least dose of study medication and had a subsequent efficacy observation. The null hypothesis was tested using ANOVA and ANCOVA. The placebo-adjusted 95% CI of orlistat treatment effect was also determined based on the LSM. Mean±sd weight change (kg) from week –4 to end of year 1 (ITT) C: -6.4±6.7 I1: -8.5±7.3 I2: -9.4±6.4 (p<0.001 for C vs I1 and C vs I2, LSM) Mean±sd weight change (kg) from week –4 to end of year 1 (completers) C: -7.0±6.8 I1: -9.6±7.3 I2: -9.8±6.3 (p<0.002 for C vs I2, LSM) C achieved significant weight loss at the end of year 1 in both the ITT and completers analyses (p<0.001)	Withdrawals during run-in 54/783 (7%) Withdrawal during year 1 C: 85/243 (35%) I1: 57/242 (24%) I2: 63/244 (26%) Withdrawal during year 2 C: 22/158 (14%) I1: 45/185 (24%) I2: 22/181 (12%) Reasons for withdrawal during year 1 (C/I1/I2) Adverse event 4 (1.6%) /16 (6.6%) /15 (6.1%) Treatment failure 5 (2.1%) /4 (1.7%) /6 (2.5%) Refused treatment 24 (9.9%) /12 (5.0%) /20(8.2%) Lost to follow-up 21 (8.6%) /12 (5.0%) /6 (2.5%) Did not co-operate 20 (8.2%) /10 (4.1%) /12(4.9%) Protocol violation 5 (2.1%) /2 (0.8%) /2 (0.8%) Entry violation 1 (0.4%) /0 (0%) /0 (0%) Administrative 5 (2.1%) /4 (1.7%) /2 (0.8%) Died during study 0 (0%) /0 (0%) /0 (0%) Total 85 (35.0%) /60 (24.8%) /63 (25.8%)	Limitations of the study, as noted by the study authors None stated Sponsorship Hoffman-La Roche

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
			Fasting insulin ≥90 pmol/L C: 103/237 (43%) I1: 111/239 (46%) I2: 93/242 (38%) DBP ≥90 mm Hg (untreated or treated) C: 47/237 (20%) I1: 63/239 (26%) I2: 45/242 (19%) DBP <90 mm Hg (treated) C: 20/237 (8%) I1: 22/239 (9%) I2: 17/242 (7%) Waist circumference ≥100 cm C: 141/237 (59%) I1: 145/239 (61%) I2: 133/242 (55%)	Mean±sd weight change (kg) from week –4 to end of year 2 (ITT) C: -4.3±7.4 I1: -6.6±8.3 I2: -7.4±7.1 (p<0.005 for C vs I1, p<0.001 C vs I2, LSM) Mean±sd weight change (kg) from week –4 to end of year 2 (completers) C: -4.3±7.5 I1: -6.8±8.4 I2: -7.6±7.0 (p=0.012 for C vs I1, p<0.001 C vs I2, LSM) At the end of year 2, mean weight loss in C was statistically significant in the ITT analysis (p<0.05) but not the completers population. >5% loss of initial weight at 1 year C: 43% I1: 61% I2: 62% (p<0.001 C vs I2) NB values read from graph >5% loss of initial weight at 2 years C: 38% I1: 55% I2: 68 % (p<0.001 C vs I2) NB values read from graph >10% loss of initial weight at 1 year C: 18.8% I1: 31.2% I2: 38.3% (p<0.002 C vs I1, p<0.001 C vs I2)	Reasons for withdrawal during years 1 and 2 (C/I1/I2) Adverse event 7 (2.9%) /24 (9.9%) /21 (8.6%) Treatment failure 8 (3.3%) /4 (1.7%) /6 (2.5%) Refused treatment 33 (13.6%) / 25 (10.3%) / 23 (9.4%) Lost to follow-up 23 (9.5%) /16 (6.6%) /11 (4.5%) Did not co-operate 24 (9.9%) /16 (6.6%) /15(6.1%) Protocol violation 6 (2.5%) /4 (1.7%) /4 (1.6%) Entry violation 1 (0.4%) /0 (0%) /0 (0%) Administrative 5 (2.1%) /12 (5.0%) /5 (2.0%) Died during study 0 (0%) /1 (0.4%) /0 (0%) Total 107 (44.0%) /102 (42.1%) /85 (34.8%) 11 participants with no follow-up assessments were excluded from the safety and efficacy analyses, and 2 additional participants, who had a follow-up safety assessment but no efficacy assessment, were excluded from the ITT analysis. Adverse events The authors reported that, with the exception of more frequent GI events in orlistat-treated patients, the adverse event profiles were similar in all 3 groups throughout the study, were generally mild to moderate, and resolved spontaneously.	

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
				Maintenance of >10% loss in year 2 C: 18.6% I1: 29.0% I2: 28.2% (p<0.05 for C vs I1 and C vs I2) Mean change in waist circumference at 1 year (cm) C: -4.7 I1: -6.0 I2: -6.2 n.s. Mean change in waist circumference at 2 years (cm) C: -3.1 I1: -4.7 I2: -5.1 P<0.05 for C vs I2 Mean±sd % change in total cholesterol from start of DB treatment (ITT) (1/2 years) C: 0.11±11.25% / 6.14±13.41% I1: -3.04±12.33%/2.04±15.38% I2: -6.45±11.90%/0.29±12.79% P<0.001 C vs I1 and C vs I2 at years 1 and 2 Mean±sd % change in LDL-C from start of DB treatment (ITT) (1/2 years) C: -1.48±16.67%/7.70±18.10% I1: -5.65±17.88%/1.28±21.53% I2: -9.68±16.08%/0.17±18.47% P<0.001 C vs I1 and C vs I2 at years 1 and 2 Mean±sd % change in HDL-C from start of DB treatment (ITT) (1/2 years) C: 14.03±18.25/14.59±20.39 I1: 14.60±18.69/16.99±22.26 I2: 10.75±17.83/14.12±21.03 P<0.05 C vs I2 at year 1	The authors reported that the GI events in the orlistat groups generally occurred early during treatment, were mild to moderate in intensity, resolved spontaneously, and were limited to only 1 or 2 episodes per patient. Number of severe GI events over 2 years C: 8 I1: 16 I2: 25 The majority of adverse events (38/49) occurred during year 1 Withdrawals due to adverse events C: 6 (2.5%) I1: 23 (9.6%) I2: 19 (7.9%) Withdrawals due to GI adverse events C: 2 (0.8%) I1: 12 (5%) I2: 9 (3.7%) Dx of breast cancer during the trial C: 1 (postmenopausal) I1: 1 patient diagnosed 36 days after randomisation I2: 3 (postmenopausal) No clinically significant changes were observed in any laboratory parameters. Treatment with orlistat had no clinically significant effect on pulse rate or ECG Vitamin supplementation C: 1 I1: 14 I2: 12 73% of the incidences of low vitamin levels occurred during year 1	

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
				Mean±sd LDL-HDL ratio (ITT) (day 1 / 1 year / 2 years) C: 3.24±1.16 / 2.81±1.00 / 3.06±1.01 I1: 3.28±1.11 / 2.70±0.95 / 2.82±0.94 I2: 3.12±1.07 / 2.64±0.94 / 2.87±1.05 P<0.001 C vs I1 at years 1 and 2, and C vs I2 at year 2; p<0.05 C vs I2 at year 1 Mean±sd % change in triglycerides from start of DB treatment (ITT) (1/2 years) C: 1.31±35.37%/5.51±37.68% I1: -0.82±34.25%/8.13±77.64% I2: -1.87±35.82%/1.47±40.80% n.s. Mean±sd VLDL-C (mmol/L) (ITT) (day 1 / 1 year / 2 years) C: 0.72±0.46 / 0.58±0.37 / 0.59±0.37 I1: 0.78±0.71 / 0.72±0.74 / 0.72±0.74 I2: 0.67±0.46 / 0.56±0.41 / 0.53±0.39 n.s. Mean±sd lipoprotein (a) (mg/L) (ITT) (day 1 / 1 year / 2 years) C: 284.14±357.93 / 296.84±389.03 / 284.29±340.52 I1: 280.22±346.07 / 266.15±337.33 / 209.31±259.77 I2: 328.54±409.07 / 257.36±316.79 / 233.14±291.71 P<0.05 C vs I2 at 1 year; p<0.001 C vs I2 at 2 years	The differences in mean plasma values for vitamins D and E and beta-carotene between orlistat-treated patients and patients taking placebo were statistically significant (p<0.001) The vitamin E-LDL cholesterol ratio increased during orlistat treatment (indicating no loss of vitamin E protection against LDL-induced atherogenesis) % affected by GI A/Es (C/I1/I2) Fatty/oily stool 4.6 / 24.2 / 31.7 Faecal urgency 5.4 / 10.0 / 14.4 Oily spotting 0.8 / 13.3 / 14.5 Increased defaecation 2.9 / 7.9 / 8.2 Faecal incontinence 1.3 / 3.1 / 7.4 Flatus with discharge 0.8 / 6.2 / 4.9 Oily evacuation 0.4 / 3.7 / 4.7 % withdrawals due to GI A/Es (C/I1/I2) Fatty/oily stool 0 / 0 / 0.4 Faecal urgency 0.4 / 1.3 / 0 Oily spotting 0 / 0 / 0.4 Increased defaecation 0 / 0.4 / 0 Faecal incontinence 0 / 1.3 / 0.4 Flatus with discharge / oily evacuation: data not available	

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
				Mean±sd DBP (mm Hg) (ITT) (day 1 / 1 year / 2 years) C: 81.2±9.8 / 79.9±11.0 / 81.2±9.9 I1: 81.5±10.3 / 79.5±10.0 / 81.71±10.3 I2: 79.5±9.4 / 78.6±10.2 / 79.9±9.5 P<0.05 C vs I2 at 1 year Mean±sd SBP (mm Hg) (ITT) (day 1 / 1 year / 2 years) C: 127.3±16.1 / 125.4±18.6 / 128.5±17.5 I1: 128.4±14.5 / 125.7±15.9 / 129.6±16.7 I2: 125.5±14.9 / 122.8±16.0 / 124.9±16.5 n.s. Mean±sd % change in FBG from start of DB treatment (ITT) (1/2 years) C: 2.23±7.45%/1.89±8.76% I1: -0.41±8.94%/-0.53±9.87% I2: 0.33±7.62%/-0.01±12.32% P<0.05 C vs I1 and C vs I2 at 1 year Mean±sd % change in fasting insulin from start of DB treatment (ITT) (1/2 years) C: -1.63±63.98/10.72±68.97 I1: -6.42±49.16/3.22±55.48 I2: -11.39±54.78/6.29±61.11 P<0.05 C vs I1 and C vs I2 at 2 years		

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
				Quality of life Orlistat-treated patients reported significantly greater satisfaction with their weight loss medication than placebo patients after 1 and 2 years ($p<0.001$ for I2 and $p<0.05$ for I1). Patients in I2 also expressed greater satisfaction both with losing weight and their weight loss programme ($p=0.011$ and $p=0.002$ respectively, at 2 years). Overall satisfaction with treatment, as expressed by the treatment index, was significantly greater among orlistat-treated patients compared with placebo at 2 years ($p<0.001$ and $p<0.05$ in I2 and I1 respectively). Orlistat-treated patients also reported less overweight distress than placebo, and this became statistically significant in I2 at 2 years ($p<0.05$). There were no significant differences between treatment groups in depression scores after either 1 or 2 years.		

Abbreviations: A/E – adverse events, ANOVA – analysis of variance, ANCOVA – analysis of covariance, BMI – body mass index, C – control group, DB – double-blind, DBP – diastolic blood pressure, dx – diagnosis, ECG – electrocardiogram, f – female, FBG – fasting blood glucose, GI – gastro-intestinal, HDL-C – high density lipoprotein cholesterol, hx – history, ITT – intention-to-treat, I1 – first intervention group, I2 – second intervention group, LDL-C – low density lipoprotein cholesterol, LOCF – last observation carried forward, LSM – least squares mean, m – male, no. – number, n.s. – not significant, SB – single-blind, SBP – systolic blood pressure, sd – standard deviation, tid – three times per day, VLDL-C – very low density lipoprotein, 95% CI – 95% confidence intervals.

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Hill et al (1999)[44] USA Aim To assess the effectiveness of orlistat in preventing weight regain. To assess the long-term effects of orlistat on obesity-related cardiovascular disease risk factors Method of randomisation Not stated. Stratification according to weight loss during run-in (≤10% or >10% of initial body weight) Outcomes Body weight; waist circumference; serum lipid levels; fasting serum glucose and insulin levels; vital signs; BP; haematology; clinical chemistry; urinalysis; levels of fat-soluble vitamins and beta-carotene; faecal fat content; adverse events. Setting and length of treatment 17 clinical research centres in the USA. 6 month run-in for weight loss followed by 1 year DB phase for weight maintenance.	Population Not stated Inclusion criteria For run-in (weight loss) Age ≥18 years; BMI 28-43 kg/m^2 For DB phase (maintenance) Loss of ≥8% of initial body weight during run-in. Exclusion criteria Hx of significant medical disorder; uncontrolled hypertension; recurrent nephrolithiasis; symptomatic cholelithiasis; active GI disorders; type 2 diabetes; pancreatic disease; cancer; pregnancy; lactation; hx or presence of substance abuse; eating disorders; excessive alcohol intake; significantly abnormal laboratory results; previous GI surgery for weight loss; hx of post-operative adhesions; taking medications known to influence body weight, appetite, or lipid levels during the 8 weeks prior to screening.	6 month run-in period for all patients (weight loss) Nutritionally balanced reduced energy diet containing 30% energy as fat, 50% as carbohydrate, and 20% as protein (deficit 4180 kJ/day to produce weight loss of 0.5-1.0 kg/wk). Deficit based on estimated energy expenditure, calculated from each individual's calculated basal metabolic rate, taking into account gender, age, and weight. Individuals given daily energy intake equivalent to their basal metabolic rate multiplied by 1.3. Participants received dietary counselling, attended a 4-session behavioural modification programme, and were encouraged to walk briskly for 20-30 minutes 5 times per week. All previous vitamin supplements discontinued; standard daily multivitamin and multi-mineral tablets prescribed. Patients were asked to record food and drink intake for 3 consecutive days at 7 time points. (n=1313)	Gender no. m/f C: 28/156 I1: 29/157 I2: 35/136 I3: 23/156 Mean±sem age (years) C: 46.4±0.7 I1: 46.8±0.8 I2: 46.1±0.7 I3: 45.9±0.7 Race no. White/Black/Hispanic/other C: 164/9/8/3 I1: 164/14/5/3 I2: 155/10/5/1 I3: 153/9/17/0 Mean±sem weight (kg) C: 90.8±0.9 I1: 89.3±0.9 I2: 92.4±0.9 I3: 89.7±0.9 I2 significantly different from other groups ($p<0.05$), accounted for by more males in the group Mean±sem BMI (kg/m^2) C: 32.8±0.2 I1: 32.6±0.2 I2: 32.9±0.2 I3: 32.8±0.2 Serum lipid levels Similar across groups	Statistical techniques ITT analysis included those who received at least one dose of medication and for whom at least one body weight measurement was taken before and after randomisation. Safety analysis included those who had received at least dose of medication and who had had at least one F/U safety evaluation. LOCF data were used. Completers' analysis included those with ≥70% adherence to drug regimen (assessed by counting returned capsules). ANCOVA used to assess between group differences in % weight regain, with weight lost during run-in as the covariate. Placebo-adjusted treatment differences and 95% CI were based on LSM. Comparisons between groups in changes in risk factor variables over time assessed with ANOVA and ANCOVA with change in body weight as the covariate. Chi-square for categorical analysis of frequency distributions. Weight loss during run-in Approx 10 kg overall Mean±sem weight change after 1 year DB treatment relative to body weight at start of run-in C: -5.93±0.69 I1: -5.15±0.55 I2: -6.16±0.49 I3: -7.24±0.52 P<0.001 C vs I3	Withdrawals during 6 month run-in 584/1313 (44%) Main reasons for withdrawal during run-in Failure to meet 8% weight loss goal 35% Lost to F/U 27% DNA appointments 14% Uncoop 9% Protocol viol 9% Withdrawals during DB study C: 50/188 (27%) I1: 47/187 (25%) I2: 40/173 (23%) I3: 55/181 (30%) No. withdrawals during DB study due to A/Es C: 5 I1: 17 I2: 17 I3: 27 No. completers C: 138 I1: 140 I2: 133 I3: 126 7 participants were excluded from the safety analysis because of no F/U safety assessments 2 participants were excluded from the ITT analysis due to no F/U efficacy assessments	Limitations of the study, as noted by the study authors Some readjustments in body weight would occur in most patients because the prescribed dietary intake was increased at the time of randomisation. As a result, this study may have underestimated the benefits of orlistat in weight maintenance. Furthermore, patients who began to gain weight were asked to maintain the higher weight rather than resume an energy reduced diet. Under actual clinical practice conditions, patients would be encouraged to reduce their energy intake. Sponsorship Hoffmann-La Roche

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
		Standard care for all patients during DB study (maintenance) Individuals' energy requirements were reassessed and an increase in energy intake was prescribed to match anticipated metabolic requirements over the ensuing year. Dietary and behavioural counselling provided throughout the year. If patients regained weight during this period, a reduced energy diet was not initiated, but they were encouraged to maintain this higher weight. Patients were asked to record food and drink intake for 3 consecutive days at 4 time points.		ITT weight loss results similar to completers Mean±sem weight regain during I year DB phase expressed as % of the weight lost during run-in C: 56.0% I1: 53.3% I2: 47.2% I3: 32.4% P<0.001 C vs I3 % weight regain expressed as % of weight lost during run-in ≤25% regain C: 29.9% I1: 32.3% I2: 30.4% I3: 47.5% P<0.05 I3 vs all other groups 25-50% regain C: 22.8% I1: 20.4% I2: 25.7% I3: 22.9% 50-75% regain C: 15.2% I1: 18.3% I2: 25.1% I3: 17.3% >75% regain C: 32.1% I1: 29.0% I2: 18.7% I3: 12.3% I2 and I3 significantly different from I1 and C (p<0.05) 23.5% of I3 patients did not regain any weight or continued to lose weight after randomisation vs. 16.3% in C. After 1 year DB phase, body weight was greater than initial body weight in 5.4% of I3 patients vs. 18.3% in C. 61.8% in I3 sustained a weight loss of >5% of initial weight vs. 49.8% in C	Adverse events During the I year DB phase, the % of patients reporting at least 1 A/E was around 7-8% greater in the orlistat groups vs. placebo. This difference was mainly accounted for by more GI events in I1, I2, and I3, with similar rates for A/Es involving other body systems across groups. % patients reporting GI events C: 68.1% I1: 82.3% I2: 91.8% I3: 95.0% Most GI A/Es were mild to moderate in intensity, occurred early during treatment, and resolved without intervention. Most patients experienced 1 or 2 episodes. Withdrawals due to GI A/Es C: 0.5% I1: 5.4% I2: 7.0 % I3: 11.7% Fat-soluble vitamins Mean levels of vitamins A, D, and E, and beta-carotene remained within the reference ranges. However, vitamin E and beta-carotene levels were significantly lower in the orlistat groups vs. placebo at the end of the study (p<0.001)	

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
		C: Placebo tid for 1 year (n=188) I1: Orlistat 30 mg tid for 1 year (n=187) I2: Orlistat 60 mg tid for 1 year (n=173) I3: Orlistat 120 mg tid for 1 year (n=181)		<u>Obesity-related risk factors after 1 year DB treatment</u> Reductions in total and LDL-cholesterol levels from initial values were significantly greater in I1, I2 and I3 vs C. Total and LDL-cholesterol levels increased in C. Changes in LDL: HDL ratio significantly different only for C vs I1. For fasting glucose and insulin levels, mean increases of 1-2% above initial values were noted in C and I1 compared with slight reductions (around 1%) in I2 and I3. Changes in BP and waist circumference did not differ significantly between groups. Faecal fat values increased in a dose-dependent manner in the orlistat groups.		

Abbreviations: tid – three times per day, DB – double blind, BMI – body mass index, hx – history, C – control group, I1 – first intervention group, I2 – second intervention group, I3 – third intervention group, no. – numbers, m – male, f – female, sd – standard deviation, LDL – low density lipoprotein, HDL – high density lipoprotein, ANOVA – analysis of variance, ANCOVA – analysis of covariance, ITT – intention-to-treat analysis, sem – standard error of the mean, vs – versus, GI – gastrointestinal, A/E – adverse events, BP – blood pressure, 95% CI – 95% confidence intervals, LSM – least squares mean, LOCF – last observation carried forward, F/U – follow-up, uncoop – did not co-operate, viol – violation, DNA – did not attend (appointments).

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Appendix 4a: Data extraction tables for data from company submissions.

[Details in blank columns and some in final column commercial in confidence]

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Roche (2000)[48] Sweden Aim To evaluate the effect of orlistat upon weight loss in obese patients with at least one associated risk factor such as hypertension, NIDDM or hypercholesterolaemia undergoing a weight management programme. Method of randomisation Central randomisation by phone and confirmed by fax. A minimisation algorithm was used to distribute prognostic factors evenly over treatment groups Outcomes Changes in body weight; waist to hip ratio; lipid profile; fasting glucose; HbA1c; insulin; BP; laboratory tests; quality of life; adverse events; compliance (counting drug capsules). Setting and length of treatment 33 primary care units in Sweden. 2-week SB run-in followed by a 12-month BD phase	Population Primary care patients Inclusion criteria Aged 18-75 year; BMI ≥28 - ≤38 kg/m^2; ≥ 1 of the following factors: fasting blood glucose ≥6.7 mmol/l at 2 occasions or NIDDM (national criteria), TPC > 6.5 and/or plasma LDL ≥4.2 mmol/l at 2 occasions or on lipid-lowering treatment, on antihypertensive treatment or newly diagnosed DBP > 90 mmHg on ≥ 2 occasions Exclusion criteria Childbearing potential and not on an accepted method of birth control; Myocardial infarction ≤ 3 months prior to entry screening; GI surgery for weight loss; active GI disease; hx of pancreatic disease; substance abuse; on appetite suppressants.					Sponsorship Hoffmann-La Roche

Abbreviations: NIDDM – non-insulin dependent diabetes, DBP – diastolic blood pressure, LDL – low density lipoprotein, hx – history, SB – single blind, DB – double blind, BMI – body mass index, TPC – total plasma cholesterol, GI – gastrointestinal; A/E: Adverse Events.

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Roche (2000)[49] Country UK <u>Aim</u> The primary object of this study was to evaluate the effect of orlistat in comparison with placebo upon weight loss in obese patients with related cardiovascular risk factors treated for 12 months, in conjunction with a mildly hypocaloric diet. The secondary objective of this study was to evaluate the effect of orlistat in comparison with placebo upon lipid profile, oral glucose tolerance testing, fasting glucose, fasting insulin, HbA_{1c} and sitting blood pressure. <u>Method of randomisation</u> Patients were randomised using a minimisation algorithm. The first criterion to be considered was the primary risk factor (hyperlipidaemia, hyperglycaemia, hypertension), followed by centre, BMI at baseline(28-35; 35-40, ≥ 40) and weight loss during the run-in (≤ 2 kg, >2 kg). <u>Outcomes</u> Efficacy outcomes: body weight, BMI, anthropometric measurements, fat composition. Number of patients who lost or gained 0-5%, 5-10% or ≥1 kg weight, lipid profile, glycaemic control, and blood pressure.	<u>Population</u> The study population was recruited from 50 centres (10 hospital centres and 40 GP centres and an additional 18 centres) <u>Inclusion criteria</u> <u>For run-in</u> BMI for both men and women: ≥28 kg/m^2; Age: 18 to 80 years old; Male or non-pregnant female (and using adequate contraception or of non-childbearing potential); and satisfying at least 1 of the following criteria: - total plasma cholesterol ≥ 5.2 mmol/l and /or plasma LDL ≥ 4.2 mmol/l at screening visit; - glucose level ≥ 8 mmol/l (2 hrs after a standard 75g glucose load) at screening visit; - sitting DBP > 90 mmHg and < 105 mmHg (for patients ≥ 65 years, the lower DBP limit was 95 mmHg) at both the screening and baseline visits; <u>Major protocol violations:</u> - Average compliance <60%. - At least 1 of the week 8, 24, 40 or 52 visits was not attended during the specified visit window with respect to the baseline visit. - Receiving medication affecting weight or appetite other than the study drug at any time during the study.					<u>Sponsorship</u> Roche

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Safety outcomes: adverse events, patient deaths, general physical examination, vital signs, pregnancy testing, laboratory evaluations. Compliance (counting the number of capsules returned at specified clinic visits). <u>Setting and length of treatment</u> Setting not specified; Length: 12 months.						

Abbreviations: BMI: Body Mass Index; SBP: systolic blood pressure; DBP: diastolic blood pressure; SB: single-blind; DB: double-blind; ECG: electrocardiogram; QoL: Quality of Life; OGTT: oral glucose tolerance test; ITT: intention-to-treat; ANOVA: analysis of variance; ANCOVA: analysis of covariance; CI: confidence interval; Gastroint: Gastrointestinal; ANS: Autonomic Nervous System; dis: disorders; C&PNS: Central & Peripheral Nervous System; Hearing & V: Hearing and Vestibular; H&L: Hemic & Lymphatic; Liver & BS: Liver and biliary system; Metabolic and N: Metabolic and Nutritional; Musculo-S: Musculo-skeletal; Myo- E,P&V: Myo-, Endo-, Pericardial & Valve; Repro: Reproductive; Resist mech: Resistance Mechanism; Resp: Respiratory; Vasc: Vascular; LOCF: last observation carried forward.

Author (year), country of origin, aim, design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Roche (2000)[50] USA Aim To evaluate the effects of orlistat on change in body weight and on sDBP in obese hypertensive patients inadequately controlled with one or more antihypertensive medications Method of randomisation Method not clearly stated Outcomes Change in body weight; sDBP; sSBP; lipid profile; waist circumference, safety, compliance (judged by capsule counts). Setting and length of treatment 41 centres in the USA. 52 week DB treatment phase	Population Not stated For DB phase BMI: ≥ 28 to ≤ 43 kg/m^2; Essential hypertension; average sDBP ≥ 95 to ≤ 109 mmHg on 2 consecutive visits; stable regimen of ≥ 1 antihypertensive medication for 12 weeks prior to study entry; current treatment with ≥ 1 antihypertensive medication; age ≥ 40 year Exclusion criteria Weight loss of > 3 kg in the 12-week period prior to entry screening; midarm girth ≥ 42 cm; use of approved or experimental weight reduction treatments; initiation or change of diuretic therapy within 12 weeks of entry; hx of significant (psychiatric) diseases; sDBP > 180 mmHg; GI surgery for weight loss; active GI disease; recent > 2 liquid stools/day; hx or presence of cancer; substance abuse; pregnant/lactating					Sponsorship Hoffmann-La Roche

Abbreviations: sDBP – sitting diastolic blood pressure, DB – double blind, sSBP – sitting systolic blood pressure, hx – history, A/E – adverse events, C – control, I – Intervention, ATII – angiotensin II, LOCF – last observation carried forward, GI: Gastro-intestinal

Appendix 5: Quality assessment tables for RCTs

No	Study	Davidson et al (1999)[41]	Drent & van der Veen (1993)[38]	Drent et al (1995)[37]	Finer et al (2000)[40]	Hauptman et al (2000)[42]
1	Method of generating sequence of randomisation	N/S	N/S	N/S	T	N/S
2	Concealed randomisation	Y	Y	Y	Y	Y
3	Selection criteria	Y	Y	Y	Y	Y
4	A priori power calculation	N/S	N/S	N/S	Y	N/S
5	Number of participants per group at baseline	224: 668	21: 23	46: 48: 45: 47	114: 114	212: 213: 210
6	Baseline comparability	Y	Y	Y	Y	Y
7	Intention of identical treatment (apart from study interventions)	Y	Y	Y	Y	Y
8	Attempt to blind patients	Y	Y	Y	Y	Y
9	Attempt to blind carers	U/C	U/C	U/C	U/C	U/C
10	Attempt to blind outcome assessors	U/C	U/C	U/C	U/C	U/C
11	Check to what extent blinding was successful Pts / carers / assessors	N/S for all	N/S for all	N/S for all	N/S for all	N/S for all
12	Description of statistical methods used	Y	Y	Y	Y	Y
13	Measures of central tendency and variance	Y	Y	Y	Y	Y
14	Adjustment for baseline imbalance	N/A	N/A	N/A	N/A	N/A
15	Methods for dealing with missing data described	Y	N	Y	Y	Y
16	Intention-to-treat analysis	Y	N	Y	Y	Y
17	Withdrawals reported	Y	Y	Y	Y	Y
18	Patient adherence assessed	Y	Y	Y (diet)	Y (run-in only)	Y (run-in only)

No	Study	Hill et al (1999)[44]	Hollander et al (1998)[46]	Micic et al (1999)[45]	Rossner et al (2000)[47]	Sjostrom et al (1998)[43]	Van Gaal et al (1998)[39]
1	Method of generating sequence of randomisation	N/S	N/S	N/S	N/S	U/C	N/S
2	Concealed randomisation	Y	Y	Y	Y	Y	Y
3	Selection criteria	Y	Y	Y	Y	Y	Y
4	A priori power calculation	N/S	N/S	N/S	N/S	Y	U/C
5	Number of participants per group at baseline	188: 187: 173: 181	159:163	60: 60	243: 242: 244	340:343	123: 122: 123: 120: 117
6	Baseline comparability	Y	Y	Y	Y	Y	Y
7	Intention of identical treatment (apart from study interventions)	Y	Y	Y	Y	Y	Y
8	Attempt to blind patients	Y	Y	Y	Y	Y	Y
9	Attempt to blind carers	U/C	U/C	U/C	U/C	U/C	U/C
10	Attempt to blind outcome assessors	U/C	U/C	U/C	U/C	Y	U/C
11	Check to what extent blinding was successful Pts / carers / assessors	N/S for all	N/S for all	N/S for all	N/S for all	N/S for all	N/S for all
12	Description of statistical methods used	Y	Y	Y	Y	Y	Y
13	Measures of central tendency and variance	Y	Y	N	Y	Y	N
14	Adjustment for baseline imbalance	N/S	N/A	N/A	N/A	N/A	N/A
15	Methods for dealing with missing data described	Y	N	N	Y	Y	Y
16	Intention-to-treat analysis	Y	Y	N	Y	Y	Y
17	Withdrawals reported	Y	Y	Y	Y	Y	Y
18	Patient adherence assessed	N/S	Y (run-in only)	Y	Y (run-in)	Y (up to 1 yr)	Y

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Appendix 5a: quality assessment tables for data from company submissions

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Legend for quality assessment checklist:

1. T – true randomisation, Q – quasi randomisation, U/C – unclear, N/S – not stated
2. Y – yes, N – no, U/C – unclear, N/S – not stated
3. Y – yes (stated), U/C – unclear, N/S – not stated
4. Y – yes, N – no, N/R – calculated numbers not recruited, U/C – unclear, N/S – not stated
5. Number in control group at baseline: number in intervention group at baseline, U/C – unclear
6. Y – yes (reported), N – no (no details reported), B – brief details only
7. Y – yes, N – no, U/C – unclear, N/S – co-interventions not stated
8. Y – yes, N – no, U/C – unclear, N/S – not stated
9. Y – yes, N – no, U/C – unclear, N/S – not stated
10. Y – yes, N – no, U/C – unclear, N/S – not stated
11. Y – yes, N – no, U/C – unclear, N/S – not stated
12. Y – yes (reported), YM – reported but inappropriate methods used, N – no (no details reported), B – brief details only
13. Y – yes, N – no
14. Y – yes, N – no, N/S – not stated
15. Y – yes, N – no, N/A – (not applicable i.e. no missing data)
16. Y – yes, N – no, U/C – unclear, N/A – not applicable
17. Y – numbers of withdrawals reported per group and with reason, Ya – numbers reported per group but not with reason, Yb – numbers reported according to reason, but not per group, N – no (not reported), N/A – not applicable
18. Y – yes, N – no, U/C – unclear, N/S – not stated

Appendix 6: Data extraction table for economic evaluations

Author (year), country of origin, type of evaluation, currency	Interventions and main clinical outcomes	Sources of data	Methods and perspective	Results	Sensitivity analysis	Additional comments
Foxcroft & Ludders, 1999[51] UK Type of economic evaluation Cost-Utility Analysis Currency British £	Intervention All: Double-blind RCT of Orlistat vs. placebo. Sjostrom et al (1998):[43] 120 mg O. tds + diet. Hypocaloric diet: 1200 kcal (30% fat), 600 kcal deficit; at the end of week 24 1000 kcal minimum, further 300 kcal reduction. 4 weeks lead-in placebo + diet; crossover in year 2 (patients reassigned to O. or placebo + eucaloric diet) Davidson et al (1999):[41] 120 mg O. tds + diet (diet not specified); sub-group received 60 mg O. tds. 4 weeks lead-in placebo + hypocaloric diet; Year 1: 120 mg O. vs placebo; Year 2: Orlistat patients reassigned to O. (120 mg/60 mg) or placebo; all patients switched to eucaloric diet) Hollander et al (1998):[46] 120 mg O tds + diet (diet not specified). 5 weeks lead-in placebo + hypocaloric diet; 1 year follow-up. All used placebo + diet as control Outcomes Mean weight loss; Number of patients who lost > 5% of initial body weight.	Efficacy data - Sjostrom et al., 1998 - Davidson et al., 1999 - Hollander et al., 1998 Prevalence, mortality, morbidity: - Health Survey for England (webpage, March 1999) - Manson et al., 1995 - NHS CRD (report 10), 1997 - McIntyre, 1998 QOL-estimates: - James et al., 1997 - Index of Health related Quality of Life (IHQL) - Fontaine et al., 1996 - Barofsky et al., 1997 - Lean et al., 1998 & 1999 - Van Gemert et al., 1998 - Karlsson et al., 1998 - Shah et al., 1994 Cost data - Quesenberry et al., 1998 - West, 1998 - Roche computer model - Portsmouth and South East Hampshire Health Authority	Systematic literature review of studies evaluating the use of O. as an adjunct to diet in the treatment of obesity. Outcomes were based on ITT analysis. Since the denominator to be used in an ITT calculation was not clear in either of the 2y RCTs, authors re-analysed the data on an ITT basis and performed sensitivity analysis for different interpretations of the ITT denominator. Health benefits were quantified in terms of changes in Quality of Life (QOL) associated with weight loss. Side effects (gastrointestinal problems and potential vitamin malabsorption) were considered mild and transient; and are summarised in an abstract but not incorporated in the analysis. Perspective: The perspective adopted was that of the NHS. Direct costs included were: outpatient appointments, GP consultations, and drugs. Indirect costs were not included.	**Costs** 1-year average cost of Orlistat treatment for 100 persons (treated for 2 years): £73,436 **Benefits** Body weight loss - additional 3-4% of initial body weight over diet alone for obese people (weight regain in year 2) - 1.9 % for Type 2 diabetes % who lost >5% over 2yr ARR= 17.5% (95% CI = 7.4%-27.3%) NNT= 6 (95% CI = 4-14) % who lost >10% over 2yr ARR= 8.6% (95% CI = 2.7%-14.8%) NNT= 12 (95% CI = 7-37) QOL-estimates: QOL values for obese patients range from 0.680 (case 1) to 0.940 (case 2) depending on the degree of disability.	The analysis seems reasonably stable to the wide-ranging parameters of the multi-way sensitivity analysis: Basic assumptions: - Benefits of weight loss are the same across the whole spectrum of obesity and weight loss. - Costs: £73,436 (sensitivity analyses: **A**: £55,618 and **B**: £88,658) - Drop out rates: 52% O. vs 57% placebo (sensitivity analyses: **C**: 33% vs 40%) - Response rates: 34.1% of completers for O. lost >10% of initial body weight vs 17.5% placebo (sensitivity analyses: **D**: 57.1% of completers for O. lost >5% of initial body weight vs 37.4% placebo) - Utility gain of 10 kg weight loss = 0.181 (sensitivity analysis: **E**: 0.076 and **F**: 0.260) Basic analysis: Cost/QALY gained = £45,881 (range: £19,452 to £55,391).	Limitations as mentioned by the authors: This report considers the effectiveness of Orlistat in achieving weight loss and reducing certain risk factors linked to adverse health events. These proxy outcomes may not fully show the benefit or dis-benefits Orlistat has on obesity related mortality and morbidity. A societal perspective may have shown greater value for money as there are potential benefits and/or savings that have not been considered, e.g. increasing the employment rate in the obese. Utilities have been calculated on the basis of the published trial results, trial data were not consistent with EMEA prescription indication for Orlistat. Therefore the cost/QALY gained figures obtained here may be different from those obtained in clinical practice.

Author (year), country of origin, type of evaluation, currency	Interventions and main clinical outcomes	Sources of data	Methods and perspective	Results	Sensitivity analysis	Additional comments
				Case 1: 0.181 QALYs per year gained with >10% weight loss. Case 2: 0.050 QALYs per year gained with >10% weight loss. (2 independent experts rated that 0.10 and 0.19 QALYs could be gained per year with 10 kg (=10%) weight loss.) Based on case 1: the number of QALYs gained in a year of 100 persons treated with O. = 1.601. **Synthesis** The incremental cost utility of Orlistat treatment is: £73,436/1.601 = £45,881 per QALY gained.	Cost/QALY gained for sensitivity analyses: A: £34,792 B: £55,391 C: £32,860 D: £35,822 E: £13,541 F: £131,918. Orlistat prescribed in primary care: £26,635 (extreme values range: £9,779 to £66,505)	

Abbreviations: O – Orlistat, ARR - Absolute Risk Reduction, NNT - number needed to treat, Vs – Versus, Yr – Year, QOL - Quality of Life, QALY - Quality adjusted Life Year, ITT - Intention to Treat, IHQL - Index of Health Related Quality of Life, EMEA - European Agency for the Evaluation of Medical Products, CI - Confidence Interval, RCT - Randomised Controlled Trial, Tds - Three times daily.

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Appendix 6a: data extraction tables for economic evaluation from company submissions

[Last 5 columns commercial in confidence]

Author (year), country of origin, type of evaluation, currency	Interventions and main clinical outcomes	Sources of data	Methods and perspective	Results	Sensitivity analysis	Additional comments
Roche (2000)[52] Country UK Type of economic evaluation Cost-Utility Analysis Currency British Pounds	Intervention: Clinical effectiveness results are derived from re-analysis of a published RCT.[43] **Outcomes** Clinical outcomes: - Effectiveness: Weight loss; change in HbA_{1c}; change in hypertension and hyperlipidaemia; Quality of Life; Blood pressure, Lipid profile; - Benefits: Life years gained (LYG), Quality Adjusted Life Year Gained (QALY) Economic outcomes: - Cost / LYG - Cost / QALY		-			

Appendix 7: Quality assessment table for economic evaluations

Study	Foxcroft & Ludders, 1999[51]
Well-defined question	+
Comprehensive description of alternatives	+
Effectiveness established	+
Relevant costs and consequences identified	+
Costs and consequences measured accurately	+
Costs and consequences valued credibly	+
Costs and consequences adjusted for differential timing	-
Incremental analysis of costs and consequences	+
Allowance made for uncertainty in estimates of costs and consequences	+
Results/discussion include all issues of concern to users	+

Legend:
+ = item properly addressed
+/- = item partially addressed
- = item not properly addressed
? = unknown

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Appendix 7a: quality assessment tables for economic evaluations from company submissions

[Commercial in confidence]

Legend:
+ = item properly addressed
+/- = item partially addressed
- = item not properly addressed
? = unknown