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Orlistat: its current status as an anti-obesity drug

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Abstract

Orlistat is a non-centrally acting anti-obesity agent that acts locally in the gastrointestinal tract to inhibit lipase, an enzyme that is crucial for the digestion of long-chain triglycerides. At the recommended dose of 120 mg three times daily, orlistat inhibits dietary fat absorption by about 30%. Over a 1-year period, obese patients taking orlistat in combination with a hypocaloric diet show a reduction of 2–5 kg over the weight decrease with placebo. When continued for a second year in combination with a weight maintenance diet, orlistat reduces weight regain compared to placebo-treated patients. Orlistat in combination with dietary intervention is also associated with beneficial effects on cardiovascular risk factors including total and low-density lipoprotein cholesterol, blood pressure and plasma glucose. It is not known if orlistat has any impact on clinical outcomes such as myocardial infarction, stroke and sudden death. Orlistat has not been compared with other anti-obesity agents.

Keywords: Obesity; Orlistat; Lipase inhibitor; Weight loss; Weight maintenance; Cardiovascular risk

1. Background

Orlistat (Xenical®, Hoffman-La Roche) is a novel non-centrally acting anti-obesity agent that acts locally in the gastrointestinal tract to inhibit pancreatic and gastric lipases, enzymes that play a crucial role in the digestion of long chain triglycerides. At the recommended therapeutic dose of 120 mg three times a day, orlistat inhibits dietary fat absorption by about 30%. Orlistat is approved for treatment of obese patients with an initial body mass index ≥ 30 kg/m^2 or those with a body mass index ≥ 28 kg/m^2 in the presence of other risk factors such as hypertension, type 2 diabetes, hyperlipidaemia and in some cases of obstructive sleep apnoea.

The National Institute for Clinical Excellence is part of the National Health Service (NHS) in the United Kingdom and its role is to provide patients, health professionals and the public with authoritative, robust and reliable guidance on current ''best practice''. The National Institute for Clinical Excellence guidelines published in June 2001 (National Institute for Clinical Excellence, 2001) give the following recommendations for the use of orlistat.

- Orlistat should only be prescribed for obese patients (who fulfil the licensing criteria) who have lost at least 2.5 kg in weight by dietary control and increased physical activity alone, in the month prior to treatment.
- When treatment is offered, arrangements should be made for appropriate health professionals (trained practice nurses and community dieticians) to offer specific concomitant advice, support and counselling on diet, physical activity and behavioural strategies.
- Continuation of orlistat therapy beyond 3 months should be supported by evidence of a loss of at least a further 5% of body weight from the start of treatment.
- Continuation of treatment beyond 6 months should be supported by evidence of a cumulative weight loss of at least 10% of body weight from the start of drug treatment.
- Treatment should not usually be continued beyond 12 months and never beyond 24 months.

The National Institute for Clinical Excellence guidelines are more restrictive than the guidelines for use that have been approved by the Federal Drug Administration in the United States. For instance, there is no requirement for prior weight loss using a hypocaloric diet and exercise alone. In

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addition, continuation of treatment beyond 3 and 6 months does not require weight loss of at least 5% and 10%, respectively.

2. Clinical pharmacology

2.1. Mode of action

Orlistat is a chemically synthesised hydrogenated derivative of lipstatin, a naturally occurring lipase inhibitor produced by *Streptomyces toxytricini* (Guerciolini, 1997). Orlistat exerts its therapeutic activity in the lumen of the gastrointestinal tract by forming a covalent bond with the active serine residue site of gastric and pancreatic lipase. The inactivated enzymes are unable to hydrolyse dietary fat in the form of triglycerides to absorbable free fatty acids and monoglycerides. As undigested triglycerides are not absorbed, the resulting caloric deficit may have a positive effect on weight control. Orlistat is highly specific for lipase and has no significant inhibitory effect on other digestive enzymes such as amylase, trypsin, chymotrypsin and phospholipases.

2.2. Pharmacokinetics

Systemic exposure to orlistat is minimal. Approximately 1% of orlistat is systemically absorbed, with single-dose studies showing plasma concentrations of intact orlistat <5 ng/ml after a single dose of 800 mg. In clinical studies involving monitoring of plasma samples, detection of intact orlistat in plasma was sporadic and concentrations were low with no evidence of accumulation (Sjöström et al., 1998). At therapeutic doses, orlistat is therefore unlikely to produce systemic lipase inhibition. A few cases of hypersensitivity (rash, urticaria and angiooedema) have been reported with orlistat treatment. However, with this exception, side-effects of orlistat do not appear to be related to systemic exposure to the drug or any components of the capsule.

After oral dosing, nearly all of the administered drug is excreted in the faeces, mostly as intact orlistat. Based on animal data, it is likely that the metabolism of orlistat occurs mainly within the gastrointestinal wall. Two metabolites have been identified in oral [^{14}C]-orlistat mass balance studies in obese patients. M1 (four-member lactone ring hydrolysed) and M3 (M1 with *N*-formyl leucine moiety cleaved), accounted for approximately 42% of the total plasma concentration. M1 and M3 have extremely weak lipase inhibitory activity (1000- and 2500-fold less than orlistat, respectively) and are considered pharmacologically inactive (Zhi et al., 1996, Zhi et al., 1999). The cumulative renal excretion of orlistat was less than 2%. Orlistat and its metabolites also undergo biliary excretion. Complete excretion (faecal plus urinary) of radiolabelled orlistat took 3 to 5 days.

2.3. Pharmacodynamics

Based on faecal fat measurements, the effect of orlistat 120 mg three times daily is seen after 2 days of treatment. On discontinuation of treatment, faecal fat usually returns to baseline, within 48–72 h. The inhibition of dietary fat absorption by orlistat is dose dependent. There is little additional effect on faecal fat excretion at doses greater than 360 mg daily and the recommended dose is one 120 mg capsule three times daily.

3. Orlistat in clinical practice

3.1. Recommendations for use

In adults, the recommended dose of orlistat is one 120 mg capsule with each main meal. The capsules may be taken immediately before, during or up to 1 h after the meal. The patient should be on a well-balanced, mildly hypocaloric diet that contains approximately 30% of calories from fat. The daily intake of fat, carbohydrate and protein should be distributed as evenly as possible over three main meals. Gastrointestinal side-effects may increase when orlistat is consumed with a meal high in fat content ($>30\%$ total daily calories from fat). The effect of orlistat on weight loss is diminished in patients consuming less than 30% of calories from fat. No dose adjustment is necessary for the geriatric patient. The safety and efficacy of orlistat has not been established in children. At least one ongoing study is attempting to determine the safety, tolerability, and efficacy of orlistat in severely obese children and adolescents with obesity-related comorbid conditions. Patients should be counselled to take a multivitamin that contains fat-soluble vitamins to ensure adequate nutrition because orlistat has been shown to reduce the absorption of some fat soluble vitamins and β-carotene. The supplement should be taken once a day at least 2 h before or after the administration of orlistat. Many physicians advise their patients to take the supplement at bedtime.

3.2. Weight loss and prevention of weight regain

The effects of orlistat on weight loss, weight maintenance, and prevention of weight regain and on a number of related comorbid conditions were assessed in eight long-term (1- to 2-year duration) multicenter, double-blind, placebo-controlled clinical trials (James et al., 1997; Hollander et al., 1998; Sjöström et al., 1998; Davidson et al., 1999; Hill et al., 1999; Finer et al., 2000; Rossner et al., 2000; Karhunen et al., 2000). Similar inclusion criteria were used in these studies. Obese (body-mass index range 28–47 kg/m^2) men and women, aged 18–77 years, were eligible for inclusion. Obese patients were randomised to placebo or orlistat (120 mg three times daily), combined with a hypocaloric diet (energy deficit of 500–600 kcal/day) dur-

Table 1
Percentage of patients losing ≥5% and ≥10% of body weight from randomisation after 1-year treatment

Study	Intent-to-treat population					
	≥5% Weight loss			≥10% Weight Loss		
	Orlistat (no. of pts in study)	Placebo (*n*)	*p*-Value	Orlistat (%)	Placebo (%)	*p*-Value
Hollander et al., 1998	48.8% (163)	22.6% (159)	<0.001	17.9	8.8	0.017
Sjöström et al., 1998	68.5% (343)	49.2% (340)	<0.001	38.8	17.7	<0.001
Davidson et al., 1999	65.7% (657)	43.6% (223)	<0.01	38.9	24.8	0.004
Finer et al., 2000	35.5% (110)	21.3% (108)	<0.05	28.0	17.0	0.02
Rossner et al., 2000	61.6% (244)	18.3% (243)	not stated	38.3	18.8	<0.001
Hauptman et al., 2000	50.5% (210)	30.7% (212)	<0.001	28.6	11.3	<0.001

Patients were treated with orlistat (120 g three times daily) or placebo in combination with a mildly hypocaloric diet.

ing the first year and in three of the trials a weight maintenance diet in the second year of treatment to prevent weight regain. The percentages of patients achieving ≥5% and ≥10% weight loss after 1 year for the intent-to-treat populations are summarised in Table 1.

3.2.1. Studies of orlistat in specialist obesity clinics

Sjöström et al. (1998) studied the efficacy of orlistat in promoting weight loss and preventing weight regain in obese patients over a 2-year period. After completing a 4-week, single blind, placebo lead-in period, 683 patients (567 women) were randomised to receive either orlistat 120 mg three times daily ($n=343$) or placebo ($n=340$) in conjunction with a hypocaloric diet (600 kcal/day less than calculated total energy expenditure) containing 30% of the energy as fat. At randomisation, the study groups were similar with mean baseline body mass index of 36.0 kg and body weight of 99.8 and 99.1 kg in the placebo and orlistat groups, respectively. To compensate for the anticipated reduction in energy expenditure accompanying the weight loss, the prescribed energy intake was further reduced by about 300 kcal/day at the end of week 24. For subjects already prescribed the minimum daily energy intake of 1200 kcal/day, daily consumption was only reduced to 1000 kcal/day. In the second 52-week double-blind period, 526 patients were reassigned orlistat or placebo with a weight maintenance (eucaloric) diet which was designed to prevent or diminish weight regain rather than to produce further weight loss. At the end of the first year, the mean decrease in body weight was 10.3 kg in the orlistat group compared with 6.1 kg in the placebo group (Fig. 1). At the end of year 1, significantly more patients in the orlistat group achieved clinically relevant weight loss (≥5%, Table 1). During the second year, patients who continued on orlistat regained about 2 kg, while those switched to placebo had regained about 4.6 kg ($P<0.001$). Patients switched from placebo to orlistat lost an additional 0.9 kg during year 2 in contrast to a mean regain of 2.5 kg in those continued on placebo

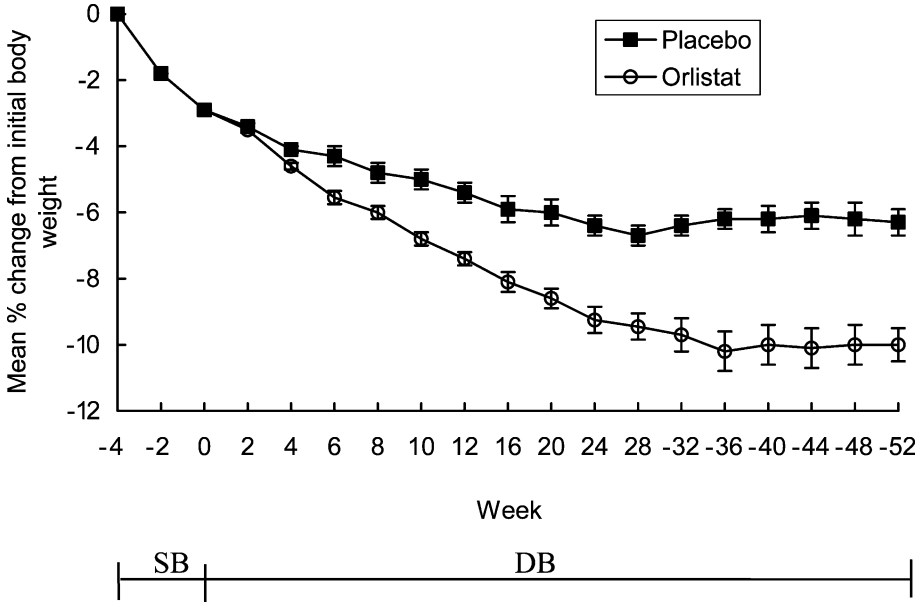

Fig. 1. Mean percentage change (± S.E.M.) in bodyweight after 1 year of orlistat or placebo treatment in combination with a hypocaloric diet (adapted from Sjöström et al., 1998). SB = single-blind lead-in period of 4 weeks; DB = double-blind, placebo-controlled treatment.

($P<0.001$). At the end of 2 years, 57.1% of orlistat patients vs. 37.4% who took placebo during both years maintained $\geq 5\%$ weight loss. It is not known if a continuous hypocaloric diet during the second year would have prevented some of the weight regain.

In a 2-year double-blind multicentre trial, 892 obese patients (30–43 kg/m^2) were randomised to receive placebo ($n=224$) or orlistat 120 mg three times daily ($n=668$) plus a hypocaloric diet (Davidson et al., 1999). At the end of the first year, patients were placed on a weight maintenance diet to assess the impact of treatment on the prevention of weight regain. In the second year those patients originally randomised to orlistat were re-randomised either to the initial dose (three times daily) of 120 mg, to a 60-mg dose, or to placebo. At the end of the first year, orlistat-treated patients lost significantly ($P<0.001$) more weight (8.7 ± 0.37 kg) than those in the placebo group (5.8 ± 0.67 kg). More orlistat-treated patients achieved clinically significant weight loss (>5% of their initial body weight) compared with the placebo-treated subjects (Table 1). Of the subjects treated with orlistat 120 mg three times daily during the first year, those who also received 120 mg during the second year regained significantly less of their first-year weight loss (3.2 kg, 35.2% regain) than those who received orlistat 60 mg (4.3 kg, 51.3% regain) or placebo (5.6 kg, 63.4% regain) during the second year ($P<0.001$). Treatment with orlistat 120 mg for 2 years produced significantly more ($P=0.02$) weight loss (7.6% of initial body weight) compared with patients who received placebo for 2 years (4.5%). In this study, the investigators also measured waist circumference, which is the best anthropometric correlate of the amount of visceral adipose tissue or intra-abdominal fat (Pouliot et al., 1994). Preferential accumulation of abdominal adipose tissue, especially of visceral adipose tissue, is an independent risk factor for the development of type 2 diabetes and coronary heart disease (Kissebah et al., 1989). After 2 years of treatment, the decrease in mean waist circumference was significantly ($P<0.05$) greater in the orlistat-treated group (-4.5 cm) compared with the placebo group (-2.4 cm).

The selection and exclusion criteria in these two studies (Sjöström et al., 1998; Davidson et al., 1999), which are the largest of several similar placebo-controlled studies, may limit extrapolation to the general population of obese patients. Subjects were excluded if they had cardiac, renal, hepatic, gastrointestinal, psychiatric, or endocrine disorders or drug-treated diabetes mellitus.

3.2.2. Orlistat in primary care

Hauptman et al. (2000) evaluated the efficacy and tolerability of orlistat in a randomised, double-blind, placebo-controlled, study conducted over 2 years in seventeen primary care centres in the United States. This study differed from others in that patients were counselled by health care staff who had no specialist training in diet or obesity management. Patients viewed videos on behaviour modification for weight loss and were provided with booklets on weight management and dieting. A total of 796 obese patients (body mass index, 30–43 kg/m^2) were randomised to receive placebo, orlistat 60 mg three times daily or orlistat 120 mg three times daily in conjunction with a reduced-energy diet for the first year and a weight-maintenance diet during the second year. Patients in each of the orlistat groups lost significantly more weight (7.1 and 7.9 kg for the 60 and 120 mg orlistat groups, respectively) than those treated with placebo (4.1 kg) in year 1 ($P<0.001$) and sustained more of this weight loss during year 2 ($P<0.001$). More patients treated with orlistat lost 5% or more of their initial weight in year 1 compared with placebo (Table 1) and this weight loss was sustained over 2 years in significantly more ($P<0.001$) of the orlistat-treated patients (34%) compared with 24% in the placebo group ($P<0.001$). Mean weight loss in this study, in both the orlistat and placebo groups, was slightly less than that achieved in other trials of orlistat.

3.2.3. Orlistat in patients with type 2 diabetes

Caloric restriction and modest weight loss (5–10% of initial body weight) improves glycaemic control and insulin sensitivity in obese patients with type 2 diabetes and is an important goal of therapy (Wing et al., 1987a; Meigs et al., 1997). However, weight loss can be difficult to achieve and sustain with dietary restriction and exercise alone in this group of patients (Hanefield et al., 1991; Wing et al., 1987a). Hollander et al. (1998) studied the efficacy of orlistat in promoting weight loss in 322 obese patients (49% female, body mass index 28–40 kg/m^2) with type 2 diabetes who were taking oral sulphonylurea drugs. Patients were randomised to orlistat 120 mg three times daily or placebo in combination with a hypocaloric diet (500 kcal/day deficit) for 1 year. Orlistat-treated patients lost significantly ($P<0.001$) more weight (6.2% of initial body weight) than the placebo group (4.3%). Twice as many patients receiving orlistat lost $\geq 5\%$ of their initial body weight (Table 1). Similarly, more patients in the orlistat group than in the placebo group lost $\geq 10\%$ of their initial body weight. Furthermore, mean waist circumference decreased significantly more ($P<0.01$) in the orlistat-treated group (4.8 cm) than in the placebo group (2.0 cm).

3.2.4. Summary

In summary, orlistat in combination with a hypocaloric diet has been shown to be efficacious in promoting weight loss over a 1-year period. In absolute terms, mean weight loss from trials shows a reduction of some 2 to 5 kg over the weight decrease with placebo. The percentage of subjects who lost more than 5% of their initial body weight ranged from 18.3% to 49.2% in the placebo groups and 35.5% to 68.5% in those treated with orlistat; greater than 10% weight loss occurred in 8.8% to 24.8% and 17.9% to 38.9% of these groups, respectively (Table 1). When continued for a second year in combination with a weight maintenance diet, orlistat reduces weight regain

compared to placebo-treated patients. There is no evidence about the efficacy of orlistat in promoting weight loss for periods over 12 months since all studies discontinued hypocaloric diets at 12 months.

3.3. Metabolic complications of obesity

Weight reduction in orlistat-treated patients is associated with beneficial changes in several cardiovascular risk factors, including dyslipidaemia, hyperinsulinaemia, glucose intolerance and type 2 diabetes. In clinical studies, the difference in serum cholesterol levels between placebo and orlistat-treated subjects was greater than would be expected from weight loss alone. The independent-cholesterol lowering effect of orlistat is thought to be related to the partial inhibition by orlistat of fat absorption from the gastrointestinal tract. The decrease in fasting glucose and insulin concentrations in orlistat-treated patients appeared to be related to the overall greater weight loss in these patients rather than an independent drug effect.

3.3.1. Dyslipidaemia

In the 2-year study by Sjöström et al. (1998), patients treated with orlistat achieved significantly greater reductions in serum total cholesterol and low-density lipoprotein cholesterol concentrations than those who received placebo. During a 4-week placebo lead-in period, weight loss was accompanied by significant decreases in total cholesterol and low-density lipoprotein cholesterol within the future placebo and orlistat groups. However, after randomisation, total and low-density lipoprotein cholesterol continued to decline in the orlistat-treated subjects but increased in the placebo group even though the subjects were losing weight. After 1 year of treatment, there was a 0.36% reduction in total cholesterol and 1.15% reduction in low-density lipoprotein cholesterol in orlistat-treated patients compared with a 4.91% and 5.18% increase in the placebo-treated patients ($P<0.001$). The group that received orlistat for 2 years showed a reduction in total cholesterol and low-density lipoprotein cholesterol (-1.14% and -0.62%, respectively compared to before treatment values). This was in contrast to those who received placebo for 2 years in whom these values increased ($+6.51\%$ and $+6.05\%$). Changes in triglyceride were similar in both groups throughout the study. A lipid-lowering effect of orlistat (Fig. 2) was also reported by Davidson et al. (1999), and in obese patients with type 2 diabetes (Hollander et al., 1998).

3.3.2. Insulin and glucose metabolism

In studies of non-diabetic obese subjects, orlistat in combination with diet resulted in significantly greater improvements in fasting serum insulin and blood glucose concentrations than treatment by dietary intervention alone. At 1 year, there was a significantly greater decrease in blood glucose in patients receiving orlistat (-0.21 mmol/l) compared with those receiving placebo (-0.07 mmol/l). At the end of the second year of the study, blood glucose was just below (-0.02 mmol/l) pre-treatment values in those who received orlistat for 2 years and had increased above pre-treatment values ($+0.25$ mmol/l) in those who received placebo for 2 years (Sjöström et al., 1998). In addition, at the end of 2 years, fasting serum insulin concentrations were lower (-5.05% compared to pre-treatment values) in orlistat-treated patients compared to those receiving placebo ($+19.1\%$). In the study by Davidson et al. (1999), orlistat in combination with diet also resulted in significantly greater improvements in levels of fasting serum insulin and glucose after 1 and 2 years than treatment by dietary intervention alone.

Heymsfield et al. (2000) pooled data from three similar orlistat trials (Davidson et al., 1999; Sjöström et al., 1998; Hauptman et al., 2000) to determine whether small amounts of weight loss improved glucose tolerance and reduced the rate of diabetes onset in obese patients. This meta-analysis included only those patients who were assigned to receive either orlistat 120 mg three times daily or placebo for the full 2 years. After 2 years, patients taking orlistat lost significantly more weight (6.7 kg; $P<0.001$) than patients taking placebo (3.79 kg). Impaired glucose tolerance at baseline was present in 18.7% and 16.8% of subjects in the orlistat and placebo groups, respectively. After 2 years, a smaller percentage of these patients progressed to diabetes in the orlistat (3.0%) vs. placebo (7.6%, $P=0.04$) group. Furthermore, of the patients with impaired glucose tolerance at baseline, 71.6% who were treated with orlistat had normal glucose tolerance at the end of treatment compared with 49.1% in the placebo group ($P=0.04$). Fasting serum glucose concentrations decreased more in patients taking orlistat than in those taking placebo whether they had normal (-0.16 vs. -0.04 mmol/l; $P=0.02$) or impaired glucose tolerance (-0.42 vs. $+0.1$ mmol/l; $P=0.01$) at baseline. There was a trend towards reduced fasting insulin concentrations in the orlistat-treated group but this was not significantly different from placebo.

Modest weight loss of 5–10% improves glycaemic control in patients with type 2 diabetes (Wing et al., 1987b). In the study by Hollander et al. (1998), obese patients with type 2 diabetes were treated with orlistat in combination with a mildly hypocaloric diet. At 1 year, there was a significant improvement in glycaemic control in the orlistat-treated group as reflected in decreases in haemoglobin A_{1c}, fasting blood glucose and in dosage reductions in oral sulphonylurea medication. Mean fasting insulin concentrations decreased in orlistat-treated patients and increased in the placebo group. However, this difference was not statistically significant (Table 2).

3.3.3. Blood pressure

Moderate weight loss of just 5 kg is associated with a significant reduction in blood pressure in obese patients with or without hypertension (Langford et al., 1991; Whelton et al., 1998). In the study by Sjöström et al. (1998),

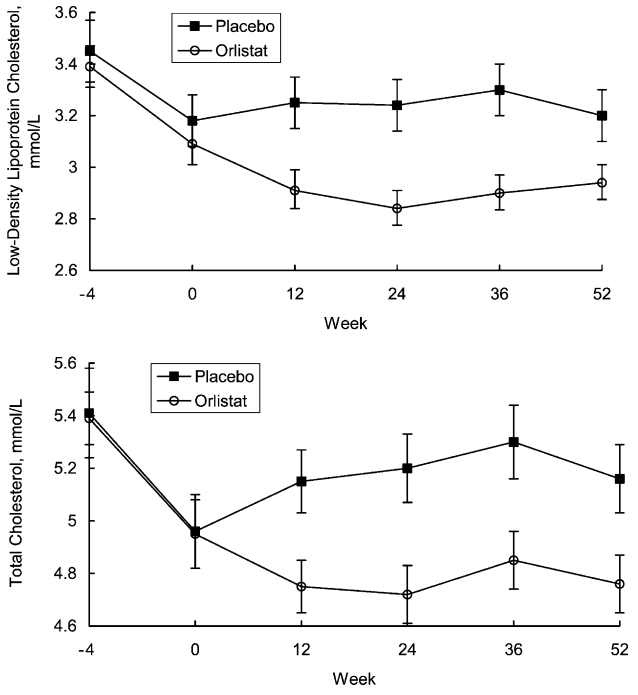

Fig. 2. Mean (± S.E.M.) changes in fasting serum low-density lipoprotein cholesterol and total cholesterol concentrations in obese patients during treatment with orlistat or placebo in combination with a hypocaloric diet (adapted from Davidson et al., 1999).

systolic and diastolic blood pressure were slightly, yet significantly, decreased in the orlistat group compared with placebo-treated patients (mean systolic 129.0 to 127.0 vs. 128.0 to 129.0 mm Hg, respectively after 1 year; $P = 0.02$; diastolic 82.4 to 80.3 vs. 81.9 to 82.1 mm Hg, $P = 0.002$). The greater reductions in blood pressure in the orlistat-treated group are consistent with the greater degree of weight loss in the orlistat-treated patients. At the end of the second year and with introduction of a weight maintenance diet, blood pressure was similar in orlistat and placebo-treated patients and had increased slightly from baseline. Davidson et al. (1999) also reported significantly greater reductions in both systolic and diastolic blood pressure after 1 year of orlistat compared with placebo. A meta-analysis of five randomised, double-blind, placebo-controlled studies showed that patients who had raised diastolic blood pressure at baseline (≥ 90 mm Hg) showed a 7.9-mm Hg reduction in diastolic pressure when treated with orlistat compared with a 5.5-mm Hg reduction in the placebo-treated group (Zavoral, 1998).

3.3.4. Summary

Orlistat in combination with dietary intervention is associated with beneficial effects on cardiovascular risk factors. In clinical trials of obese patients total cholesterol, low-density lipoprotein cholesterol, low-density lipoprotein/high-density lipoprotein ratio, and concentrations of glucose and insulin decreased more in orlistat-treated than in placebo-treated patients. These changes were also apparent in obese patients with type 2 diabetes. However, it is not known if these modest changes in physiologic risk factors translate into meaningful improvements in clinical outcomes such as myocardial infarction, stroke and sudden death.

3.4. Adverse effects

The safety of orlistat has not yet been established beyond 2 years. Orlistat is not appreciably absorbed and systemic adverse events are negligible. Orlistat is associated with a greater incidence of gastrointestinal side-effects that relate to its pharmacological mode of action. The majority of patients treated with orlistat experienced 1 or 2 adverse gastrointestinal events, which usually occurred early in treatment (within 3 months), were mild to moderate in intensity, and generally resolved spontaneously (Table 3). Gastrointestinal side-effects may increase when orlistat is taken with a diet high in fat (>30% total daily calories from fat) or if the recommended daily fat intake is not distributed over three meals. In placebo-controlled trials, between 1.1% and 6% of orlistat-treated patients and 0.6% and 1.3% of placebo-treated patients withdrew because of gastrointestinal side-effects (James et al., 1997; Hollander et al., 1998; Sjöström et al., 1998; Davidson et al., 1999; Finer et al., 2000; Rossner et al., 2000).

In clinical trials, treatment with orlistat was associated with a reduction in mean blood pressure. However, there are occasional case reports of orlistat associated with increased blood pressure. In one patient, rechallenge with orlistat confirmed a temporal relationship between drug treatment and an increase in blood pressure (Persson et al., 2000, 2001).

Vagal cholinergic and cholecystokinin mediated hormonal mechanisms are the most important mediators of

Table 2
Mean changes in body weight and glycemic control from randomisation following 1-year treatment in patients with type 2 diabetes (Hollander et al., 1998)

	Orlistat ($n = 163$)	Placebo ($n = 159$)	p-Value
Weight loss (kg)	-6.19 ± 0.51	-4.31 ± 0.57	< 0.001
(%)	-6.20 ± 0.5	$-4.3 \pm 0.5\%$	
Fasting plasma glucose (mmol/l)	-0.02 ± 0.14	$+0.54 \pm 0.15$	< 0.001
HaemoglobinA_{1c} (%)	-0.28 ± 0.09	$+0.18 \pm 0.11$	< 0.001
Fasting plasma insulin (%)	-5.2 ± 4.4	-4.3 ± 6.3	NS
Percentage of patients who decreased dose of oral sulphonylurea	43.2	28.9	< 0.01
Percentage of patients who discontinued dose of oral sulphonylurea	11.7	7.5	< 0.01

gallbladder emptying under physiological conditions. The release of cholecystokinin from the small intestine is critically dependent on the presence of long-chain free fatty acids in the intestine. Postprandial cholecystokinin release and gallbladder contraction might therefore be decreased by orlistat, potentially resulting in an increased risk of gallstone formation. In healthy volunteers, orlistat in combination with a fat meal is reported to reduce (Schwizer et al., 1997; Borovicka et al., 2000; Feinle et al., 2001) or have no effect (Froehlich et al., 1996) on postprandial cholecystokinin release. In the latter study, gallbladder contraction was also measured and the investigators reported that a single dose of orlistat did not reduce gallbladder motility after ingestion of a pure-fat or mixed meal. In a double-blind controlled trial, 23 obese patients were randomised to orlistat, 120 mg three times daily or placebo in conjunction with a hypocaloric diet (Trouillot et al., 2001). At the end of the 4-week treatment period, there were adverse changes in biliary lipid composition in the placebo (decrease in total bile acid and phospholipid concentration) but not the orlistat group. Mean changes from the baseline in cholesterol saturation and gallbladder motility were similar in both groups. Microscopy of bile did not show evidence of biliary sludge in either group. Thus, in summary, short-term studies in healthy volunteers and obese patients do not suggest an increased risk of gallstone formation during treatment with orlistat. However, the safety of long-term treatment with orlistat with respect to gallstone formation remains to be determined.

Feinle et al. (2001) showed that postprandial plasma cholecystokinin levels were reduced after orlistat treatment and this was associated with an increase in hunger and a decrease in fullness measured by visual analogue scales. The authors hypothesise that an increase in hunger in patients taking orlistat could partially offset the benefit of the drug on weight loss.

During 2-year clinical studies, plasma concentrations of fat soluble vitamins (A, D, E and beta-carotene) decreased among subjects taking orlistat but generally remained within the clinical reference range. In the study by Sjöström et al. (1998), 11.9% of patients in the orlistat group and 5.3% in the placebo group had two or more consecutive low vitamin concentrations recorded in the first year of treatment. In the study by Davidson et al. (1999), treatment with orlistat was also associated with a slightly higher incidence of reduced fat soluble vitamin concentration. In this study, vitamin supplementation was required in 14.1% of subjects treated with orlistat for 2 years compared with 6.5% of placebo recipients. Supplementation with once-daily multivitamins restored serum concentrations to within the normal range and no subjects were withdrawn due to low values.

Some patients may develop increased urinary oxalate excretion following treatment with orlistat and therapy should be used cautiously in patients with a history of hyperoxaluria or calcium oxalate nephrolithiasis.

Table 3
Pooled data on the incidence of common gastrointestinal adverse events during year 1 and year 2 of treatment in clinical trials (with permission from Ballinger, 2000)

Adverse event	Year 1		Year 2	
	Orlistat (%)	Placebo (%)	Orlistat (%)	Placebo (%)
Oily spotting	27	1	4	0
Abdominal pain	26	21	–	–
Flatus with discharge	24	1	2	0
Faecal urgency	22	7	3	2
Fatty/oily stool	20	3	6	1
Increased defaecation	11	4	3	1
Faecal incontinence	8	1	2	0

3.5. Drug interactions

Absorption of fat soluble vitamins may be decreased by orlistat. In short-term studies, orlistat did not result in any change in warfarin pharmacokinetics or pharmacodynamics. However, because of a potential decrease in vitamin K absorption, patients stabilised on warfarin should be closely monitored for changes in coagulation parameters. Orlistat markedly decreased peak and trough blood cyclosporine concentrations in a transplant patient (Nagele et al., 1999). No drug interaction studies have been conducted with orlistat and cyclosporine.

3.6. Contraindications

There are no adequate and well-controlled studies of orlistat in pregnancy. Teratogenicity studies conducted in rats and rabbits at doses of up to 23 and 47 times the human dose showed no evidence of teratogenicity or embryotoxicity. However, because animal studies are not always predictive of human response, orlistat is contraindicated during pregnancy. It is not know if orlistat is secreted in breast milk and therefore orlistat should not be taken by breastfeeding women. Absolute contraindications to orlistat include chronic malabsorption syndrome or cholestasis and known hypersensitivity to orlistat or any of its components.

3.7. Summary

Orlistat inhibits gastrointestinal lipase and reduces absorption of dietary fat by about one-third. In a series of 1- and 2-year randomised placebo-controlled clinical trials, orlistat in combination with a weight-reducing diet resulted in significantly greater weight loss than that achieved with diet alone. Weight regain after a period of weight loss is also reduced by orlistat treatment. Orlistat treatment is associated with an improvement in serum lipid values that

is more than can be explained by weight reduction alone. Improvements in glycemic control and blood pressure have also been noted and result from decreases in body weight alone.

It is not known how quickly weight is regained on cessation of orlistat treatment. Longer-term studies with orlistat will also define the potential for maintenance of weight reduction and the progression to co-morbidities. In clinical studies, entry criteria included a body mass index of ≥ 28 kg/m^2 and the majority of patients enrolled were women (>82%). It is argued that high-risk obese patients should be identified on the basis of both body weight and waist circumference (Després, 2001). Men are generally characterised by the more dangerous, abdominal obesity (Després et al., 2001). Further studies are needed to define the role of orlistat in these high-risk patients.

Sibutramine is also available for the treatment of obesity. In clinical trials, sibutramine in combination with a hypocaloric diet is more effective at promoting and maintaining weight loss than dietary treatment alone. There are also associated beneficial effects on plasma concentrations of high-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, and triglyceride, but not low-density lipoprotein cholesterol, and these changes exceeded those expected from weight loss alone (James et al., 2000). Orlistat and sibutramine have not been directly compared in clinical trials.

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