Drugs 1998 Aug; 56 (2): 241-249
0012-6667/97/0008-0241/$09.00/0

Orlistat

Wendy McNeely and *Paul Benfield*

Adis International Limited, Auckland, New Zealand

Contents

Abstract

▲ Orlistat (tetrahydrolipstatin) is an inhibitor of pancreatic and other lipases. As a pancreatic lipase inhibitor, it acts in the gastrointestinal lumen and is indicated for use in obesity.

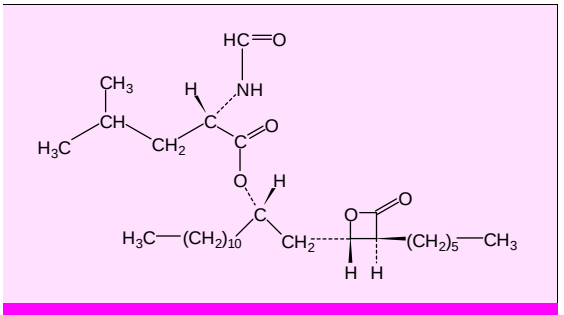
▲ Serum total cholesterol and low density lipoprotein-cholesterol levels were reduced in obese, but otherwise healthy, patients during ≤2 years' orlistat treatment; serum triglyceride and high density and very low density lipoprotein-cholesterol levels were unchanged in trials of ≤12 weeks.

▲ Obese patients who were maintained on a hypocaloric diet and who received orlistat 360 mg/day for 12 weeks lost a significantly greater percentage of bodyweight than placebo recipients (5 *vs* 3.5%).

▲ In 2-year studies, weight loss was significantly greater in orlistat than in placebo recipients by the end of year 1; weight was further reduced or maintained in the second year, when a eucaloric diet was allowed, in orlistat but not placebo recipients.

▲ A greater proportion of orlistat than placebo recipients lost >5% or >10% of their initial bodyweight in 1- and 2-year studies.

Features and properties of orlistat (tetrahydrolipstatin)	
Indication	
Obesity	Launched
Mechanism of action	
Inhibitor of intestinal fat absorption	Inhibitor of pancreatic and other lipases
Dosage and administration	
Recommended daily dosage	120mg 3 times daily with meals
Route of administration	Oral
Pharmacokinetic profile	
Plasma concentration	Below detection threshold (i.e. <5 μg/L)
Elimination half-life	14 to 19h
Drug interactions	
Drugs with a narrow therapeutic range used to treat epilepsy, diabetes mellitus or cardiovascular disease	Pharmacokinetic profiles of some of these drugs unaltered with concomitant single-dose orlistat
Adverse events	
Most frequent	Increased defecation, soft/liquid stools, oily/fatty evacuation, abdominal pain



Orlistat

Although its aetiology is not well understood, obesity is becoming more widely accepted as a chronic disease with genetic and neurological associations rather than a state resulting from a lack of will power.[1] Obesity [body mass index (BMI) >27.8 kg/m^2 for men and >27.3 kg/m^2 for women] is a risk factor associated with other chronic diseases such as diabetes mellitus, hypertension and coronary heart disease;[2] these diseases may require life-long pharmacological intervention.

Despite an increased prevalence of obesity in the US over the last 10 years, very few anti-obesity agents have been approved by the FDA.[3] One reason is that many early drugs used as appetite suppressants were classified by the Drug Enforcement Agency as schedule II controlled substances (i.e. having potential for abuse and dependency).[4] Newer anti-obesity drugs have shown little potential for abuse.[4]

Drugs used to treat obesity may be categorised according to whether they reduce energy intake, increase energy expenditure, or reduce absorption of nutrients.[5] Orlistat (tetrahydrolipstatin) is a new orally administered agent which falls into the last category. It is a partially hydrated derivative of endogenous lipstatin produced by *Streptomyces toxytricini*.[6,7] The drug is a specific and long-acting inhibitor of lipases,[6,8] and pharmacokinetic studies suggest its effects are restricted to the gastrointestinal tract,[9] where it prevents the lipase-catalysed breakdown and subsequent absorption of about one-third of dietary ingested fats.

1. Pharmacodynamic Profile

- *In vitro*, the half maximal inhibition of lipase activity was effected by similar concentrations of orlistat in mice (0.27 mg/L), pigs (0.11 mg/L) and humans (0.12 mg/L).[8] The respective median inhibitory concentration (IC_{50}) values for orlistat and lipstatin, its parent compound, for *in vitro* porcine pancreatic lipase inhibition of trioleate were 0.36 and 0.14 μmol/L.[7]

- In normal healthy volunteers consuming 60 g/day of fat, orlistat 360 mg/day recipients (n = 5) excreted 21.5 g/day more faecal fat than placebo recipients (n = 3) [BMI and duration of treatment not reported]. Increasing the dosage of orlistat from 360 to 600 mg/day did not significantly increase the efficacy of the drug as assessed by the amount of fat excreted in the faeces.[10] Furthermore, with orlistat 600 mg/day, increasing the amount of dietary fat from 60 to 76 g/day increased the absolute amount, but not the percentage, of faecal fat excreted. Approximately 32% of ingested fat was lost in the faeces of orlistat recipients and 4.4% in placebo recipients.

- Dietary fibre content (28 *vs* 10 g/day) did not influence faecal fat excretion after orlistat 80mg 3 times daily in healthy male volunteers.[11]

- Over an 8-day period, the effect of orlistat 80mg 3 times daily on faecal fat excretion was not influenced by administration time relative to meals: the agent was given to 24 healthy volunteers mid-meal or 1 or 2 hours after the meal.[12]

- In a clinical trial, 173 non-obese patients with primary hyperlipidaemia were given orlistat 30 to 360 mg/day or placebo for 8 weeks. Figure 1 illustrates the effects of orlistat 360 mg/day or placebo on a range of serum lipid and lipoprotein levels. In orlistat ≥90 mg/day recipients decreases of approximately 6 to 10% were seen in some serum cholesterol levels [$p \leq 0.002$ for total cholesterol and $p \leq 0.02$ for low density lipoprotein (LDL)-cholesterol, both *vs* baseline];[13] corresponding increases of 1% each were seen in placebo recipients. Baseline values were measured after a 6-week placebo run-in period.

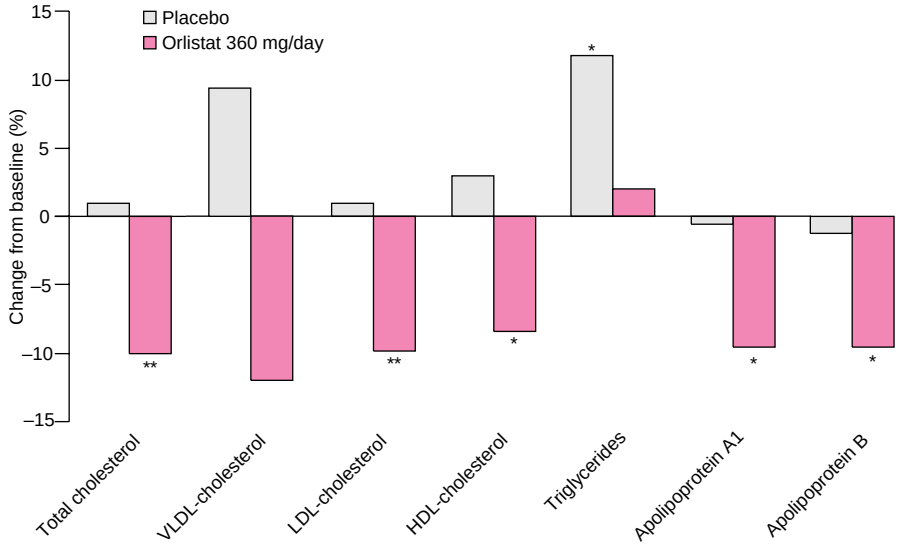


Fig. 1. Effect of orlistat 360 mg/day or placebo for 8 weeks on serum lipid and lipoprotein levels in patients with primary hyperlipidaemia.[13] Baseline values were measured after 6 weeks' placebo administration. **LDL** = low density lipoprotein; **HDL** = high density lipoprotein; **VLDL** = very low density lipoprotein;* $p < 0.05$, ** $p \leq 0.001$ *vs* baseline.

Serum total cholesterol and LDL-cholesterol levels returned to within 2% of baseline values at the end of a 2-week placebo follow-up period in all patients. Levels of serum triglycerides were essentially unchanged from baseline levels after 8 weeks' orlistat treatment, however, an approximate 12% increase in serum triglyceride levels was observed in the placebo group ($p < 0.05$ *vs* baseline). Very low density lipoprotein (VLDL)-cholesterol and high density lipoprotein (HDL)-cholesterol levels were decreased by 12 and 8% after 8 weeks' orlistat 360 mg/day therapy ($p < 0.05$ *vs* baseline for VLDL-cholesterol). In addition, orlistat 30 to 360 mg/day, but not placebo, decreased the levels of apolipoprotein A1 and B from baseline by about 3 to 10% ($p < 0.05$).

- Fasting and postprandial plasma lipid levels were altered after 8 weeks' orlistat administration (30 to 360 mg/day) in non-obese patients with hyperlipidaemia.[14] Patients were maintained on a low fat, low cholesterol (<300 mg/day) diet. Mean plasma total cholesterol, LDL-cholesterol and apolipoprotein B levels were decreased by, respectively, 7.7, 8.9 and 9.8% ($p \leq 0.006$) in orlistat recipients. However, in the placebo group, plasma and LDL-cholesterol levels were not significantly altered. Postprandial plasma triglyceride levels were measured after 8 weeks of orlistat administration and 2 weeks later after a placebo follow-up period. After a fat load [cream (40% fat emulsion; 50 g/m^2 body surface) plus 120 000IU aqueous retinyl palmitate] postprandial triglyceridaemia decreased by 27% during orlistat administration compared with the follow-up period ($p = 0.04$), but was not significantly altered in placebo recipients.

- 186 obese, but otherwise healthy, patients (BMI 27.3 to 35 kg/m^2) received placebo, or orlistat 30, 180 or 360 mg/day, for up to 12 weeks. Compared with baseline, the respective changes in serum total cholesterol levels were +0.22, +0.10, –0.10 ($p = 0.011$ *vs* placebo) and –0.22 mmol/L ($p = 0.001$ *vs* placebo).[15] Similarly, the effects of orlistat 180 or 360 mg/day on serum LDL-cholesterol levels were also significant *vs* placebo [–0.14 ($p = 0.012$) and –0.19 ($p = 0.003$), respectively, *vs* +0.13 mmol/L]. No significant changes were observed in serum

• In several 2-year studies in obese, but otherwise healthy patients (n = 688 to 892), total cholesterol and LDL-cholesterol levels were reported to be lower in orlistat 180 to 360 mg/day recipients than in placebo recipients by the end of the first year ($p < 0.05$,[16] no p-value provided[17]); in 1 study reductions were 6.5 and 9.7% for total and LDL-cholesterol levels ($p < 0.002$ *vs* placebo).[18] Reduced cholesterol levels were maintained for the duration of the study. Furthermore, patients who were switched from placebo to orlistat treatment at the end of the first year had an immediate onset and sustained decrease in total and LDL-cholesterol levels (by 6.1 and 7.9% at the end of year 2).[17] Conversely, corresponding increases of 5.2 and 8.6% occurred in patients who were switched from orlistat to placebo during the second year.

Similar decreases in baseline levels of LDL-cholesterol were observed during the 4-week run-in period in patients receiving orlistat (3.1%) or placebo (4.1%); a further 7.5% decrease and a 4.9% increase occurred, respectively, in orlistat and placebo recipients after 2 years' continued therapy.[17]

• In obese patients with type 2 diabetes mellitus (non-insulin-dependent diabetes mellitus), mean HbA_{1c} (predominant glycosylated haemoglobin; an indicator of hyperglycaemia) levels decreased from about 8% to 7.5% during a 2-week run-in period in both orlistat (120mg 3 times daily; n = 163) and placebo (n = 159) recipients. After 1 year, mean HbA_{1c} levels decreased by 0.2% and increased by 0.3%, respectively, in orlistat and placebo recipients ($p < 0.0002$). In addition, mean LDL-cholesterol levels, which decreased by 61 mg/L in both groups during the run-in period, were further decreased by 46 mg/L in orlistat recipients and increased by 82 mg/L in placebo recipients during treatment. Furthermore, in patients with an initial LDL-cholesterol level >1300 mg/L, those receiving orlistat had a mean decrease of 140 mg/L compared with a mean increase of 20 mg/L in patients receiving placebo. These results suggest that orlistat may help improve glycaemic control and dyslipidaemia in obese patients with type 2 diabetes mellitus.

• There was no significant difference in plasma thyroid hormone levels in 14 moderately obese, but otherwise healthy, patients who received either 12 weeks' orlistat 360 mg/day or placebo.[19]

• In 6 healthy volunteers, neither gallbladder motility nor release of cholecystokinin was altered by a single 200mg dose of orlistat.[20]

2. Pharmacokinetic Profile

• In an overview of phase I single-dose studies in healthy volunteers or obese patients (n = 6 to 12),[9] plasma orlistat concentrations, measured over a period of 1.5 to 69 hours after administration of 50 to 800mg of the drug, were <5 μg/L (the assay limit of detection). In multiple-dose studies (orlistat 25 to 400mg 3 times daily for 5 to 23 days), plasma drug concentrations, measured up to 96 hours after initial orlistat administration, were similar to those seen after single-dose studies. However, in 1 study (n = 6 obese volunteers; orlistat 1200 mg/day for 10 days) 3 plasma orlistat concentrations of >4 μg/L and <50 μg/L were reported.

• In 2 similar studies, healthy male volunteers (n = 6 and 8) received single-dose [^{14}C]orlistat 50 or 350mg.[9] Maximum plasma radioactivity levels were measured at 7.5 or 8.2 hours after administration. However, plasma orlistat concentrations were below the limit of detection (i.e. <5 μg/L) throughout both studies. Although 4 and 1.5% of the total radioactivity was recovered in the urine no intact orlistat was detected. The remainder of the total radioactivity was recovered in the faeces within 4 days' administration of radiolabelled drug; up to 83% of this was attributable to intact orlistat. These data suggest limited systemic absorption and metabolism of the agent. Elimination half-life values of 14 to 19 hours were reported for orlistat.

Effects of Orlistat on the Pharmacokinetics of Other Drugs

• In a number of crossover studies in healthy volunteers (n = 12 to 18), the pharmacokinetic profiles of single-dose digoxin (0.4mg),[21] nifedipine sustained release (60mg),[22] phenytoin (300mg)[23] or

glyburide (5mg)[24] were not significantly altered when these drugs were given concomitantly with orlistat 240 to 360 mg/day for 6 to 16 days. The time to maximum plasma concentration for R-warfarin (given as 30mg racemic warfarin sodium) was greater in the presence of orlistat than with placebo (3.5 *vs* 2.5 hours); all other pharmacodynamic parameters of warfarin measured in the study were similar in placebo and orlistat recipients.[25]

- In healthy volunteers (n = 6 to 8 per group), the pharmacokinetic profiles of a number of antihypertensive agents including atenolol (100mg), furosemide (40mg), nifedipine (20mg) and captopril (50mg), given as single doses, were not clinically significantly altered by concomitant administration of orlistat (150 mg/day).[26]

- In 10 healthy women, orlistat 360 mg/day did not influence the action of oral contraceptives.[27]

Effects of Orlistat on the Pharmacokinetics of Dietary Supplements

Orlistat inhibits the absorption of ingested fats. It is possible, therefore, that endogenous levels of fat-soluble vitamins may become depleted with prolonged use of the agent.

- Orlistat 360 mg/day for 9 days, compared with placebo, decreased the maximum plasma concentration and the area under the concentration-time curve values of oral vitamin E acetate supplementation (400IU given on day 4 of orlistat administration) by 43 and 60%, respectively. This suggests that short term administration of orlistat may compromise vitamin E absorption from the gut. Conversely, the pharmacokinetic profile of oral vitamin A acetate supplementation (25 000IU given on day 4 of orlistat administration) was not significantly affected.[28]

- Small, clinically insignificant decreases in serum levels of vitamins A and D were seen in obese patients after 12 weeks' treatment with placebo or orlistat 30 to 360 mg/day:[15] vitamin A levels decreased by 0.034 μmol/L in the placebo group and by between 0.004 and 0.095 μmol/L in the orlistat group; the corresponding reductions in vitamin D levels were 15.4 nmol/L and between 12.1 and 23.3 nmol/L. The reduction in vitamin D levels observed in both placebo and orlistat groups was attributed to seasonal change (from autumn to winter). Vitamin E levels were significantly reduced with orlistat 180 and 360 mg/day (by 3.16 and 3.48 μmol/L) and increased with placebo (by 0.81 μmol/L; all $p < 0.01$).

- Approximately 60% of a supplemental dose of β-carotene, a major dietary source of vitamin A, was absorbed when a single 30 to 120mg dose was given (on day 4) to 12 healthy volunteers receiving orlistat 360 mg/day.[29] This may be sufficient to achieve physiological levels of β-carotene in obese patients who may develop reduced levels of the agent during orlistat therapy.

- Meta-analysis of obese patients who received orlistat 360 mg/day (n = 2038) or placebo (n = 1740) for up to 2 years, revealed that plasma levels of vitamins D and E and β-carotene were significantly reduced in orlistat compared with placebo recipients; the levels, however, remained within the normal clinical range (no further details provided).[30]

3. Therapeutic Trials

In the studies reviewed, patients were obese, but healthy unless stated otherwise. The trials followed a randomised, double-blind, placebo-controlled design. In studies of ≤1 year in duration, patients received a mildly hypocaloric diet (500 to 800 kcal/day deficit, typically, with 30% of calories from fat) in conjunction with study medication; a eucaloric diet was allowed in the second year of the 2-year studies.

- 135 obese patients (BMI 27.3 to 35 kg/m^2) completed a 12-week study in which they received placebo or orlistat 30 to 360 mg/day.[15] During a 4-week run-in period, on placebo and a reduced calorie intake, weight loss was similar in all patients. After 12 weeks' therapy, however, weight loss was 3.5, 3.9, 4.1 and 5%, respectively, for pla-

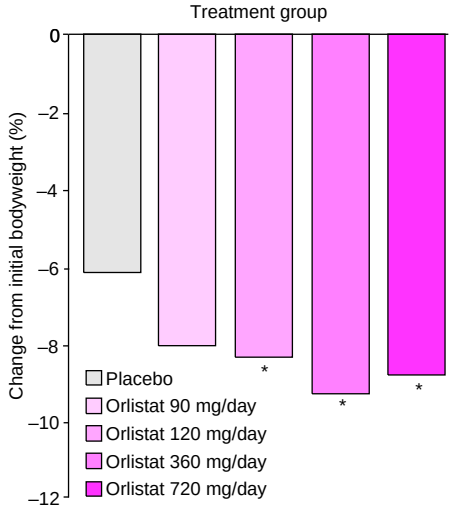


Fig. 2. Dose-related effect of orlistat on weight loss in 676 obese, but otherwise healthy, patients (BMI 28 to 43 kg/m^2). Orlistat or placebo was given 3 times daily with meals for 6 months.[31] **tid** = 3 times daily; * $p \leq 0.002$ *vs* placebo.

cebo and orlistat 30, 180 and 360 mg/day recipients ($p = 0.009$ *vs* placebo for 360 mg/day).

- Actual weight loss was greater in obese patients (BMI 27.3 to 35 kg/m^2) who received orlistat 360 mg/day for 12 weeks than in those who received placebo (n = 7 per group; 4.2 *vs* 3.0kg) but the difference between these small groups was not significant. The percentage weight loss was approximately 4% in each group.[19]

- In a 6-month dose-finding study, an intent-to-treat analysis of 605 obese patients (BMI 28 to 43 kg/m^2), revealed that orlistat 120mg 3 times daily with meals was the optimal dosage regimen (fig. 2).[31] Mean percentage weight loss from initial bodyweight was 8.5, 8.8, 9.8, 9.3, and 6.5%, respectively, after 6 months' treatment with orlistat 30, 60, 120, 240mg 3 times daily or placebo. Weight loss was significantly different from placebo in all but the 30mg group ($p \leq 0.002$). In addition, 28 to 38% of orlistat recipients compared with 19% of those who received placebo lost >10% of their initial bodyweight (IBW).

- Obese patients with type 2 diabetes mellitus randomised to receive orlistat 120mg 3 times daily (n = 163) or placebo (n = 159) for 1 year lost 6.2 and 4.3% of their IBW ($p < 0.001$). In addition, 49% of orlistat compared with 23% of placebo recipients lost >5% of their IBW.[32]

- In a 2-year study 688 obese patients (BMI 30 to 43 kg/m^2) received placebo or orlistat 120mg 3 times daily.[17] At 1 year orlistat compared with placebo recipients lost a significantly greater percentage of their IBW (10.2 *vs* 6.1%; $p < 0.05$). Furthermore, twice as many orlistat as placebo recipients lost >10% of their IBW (38.8 *vs* 17.6%; $p < 0.05$).

Weight regain was less in patients who received 2 years' orlistat treatment (26% regain of weight lost) than those receiving placebo for 2 years (43%). Moreover, patients who were switched from placebo to orlistat in the second year lost weight, whereas those switched from orlistat to placebo gained weight (52%) more rapidly than patients maintained on the drug for 2 years.

- In a second 2-year study (n = 892), after 1 year patients who received orlistat 120mg 3 times daily lost significantly more weight than placebo recipients (8.8 *vs* 5.8%; $p < 0.05$). Mean weight regain was less in patients maintained on orlistat than on placebo for the second year (35 *vs* 63%; $p < 0.05$). In addition, 44.4% of orlistat recipients lost >5% of their IBW in the first year and either lost further weight, or regained <25% of the lost bodyweight during the second year.[16]

- Weight loss in patients receiving orlistat 120mg 3 times daily was maintained in the second year of another 2-year study (n = 792).[18] At 1 year, orlistat-treated patients had lost a greater amount of their IBW than placebo recipients (9.7 *vs* 6.6%; no p-values provided). Indeed, 62.5% of orlistat recipients lost >5% and 38.3% lost >10% of their IBW; the corresponding percentages for placebo recipients were 43.6 and 18.8% (no p-values provided). At year 2, mean loss of IBW was 7.6 and 4.5% for orlistat and placebo recipients. Furthermore, 51.7% and 30.3% of orlistat and placebo recipients maintained a >5% weight loss in the second year.

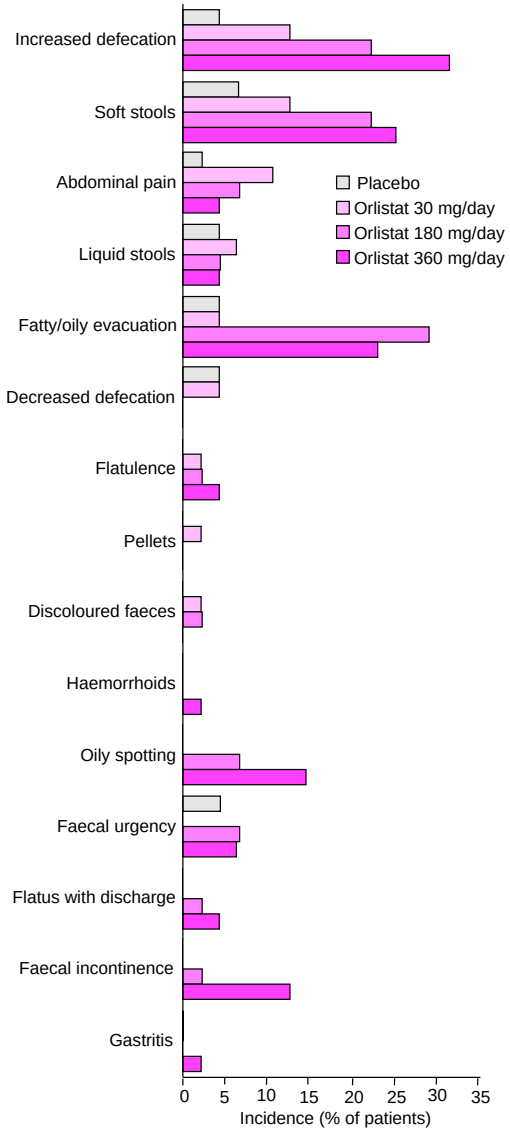


Fig. 3. Gastrointestinal adverse events reported in 188 obese patients receiving placebo or orlistat 30 to 360 mg/day for 12 weeks (no statistical details provided).[15]

4. Tolerability

• Orlistat 75 mg/day was 'better tolerated' (no further details provided) by healthy volunteers when the dietary fat content was reduced from 130 to 110 g/day.[10] Adverse events observed with orlistat therapy result from the inhibition of fat absorption rather than the drug itself. Adverse events were similar in placebo and orlistat recipients when dietary fat was reduced from 130 to 45 g/day and the agent was administered 2 hours before food (i.e. with little or no fat content in the stomach).

• Adverse events commonly observed in 188 obese patients receiving placebo or orlistat 30 to 360 mg/day are shown in figure 3.[15] Most adverse events were mild to moderate; however, abdominal pain, fatty/oily evacuation, and faecal incontinence were severe in 2.1 to 6.3% of patients receiving orlistat 360 mg/day, and oily spotting was severe in 2.2 or 4.2% of patients receiving orlistat 180 or 360 mg/day. Withdrawal from treatment because of gastrointestinal adverse events was seen only with orlistat 360 mg/day.

• Meta-analysis of results from obese patients who received placebo (n = 1740) or orlistat 120mg 3 times daily with meals (n = 2038) revealed that significant differences in the incidence of adverse events were reported for the gastrointestinal tract only.[30] Most of the adverse events reported were mild and occurred within the first week of treatment, and the incidence was reduced after 12 weeks' therapy. Furthermore, in long term studies, an 8 to 27% incidence of gastrointestinal adverse events reported by orlistat recipients in the first year decreased by between 6 and 22% during the second year. A total of 29% of orlistat and 35% of placebo recipients withdrew prematurely from studies during the first year; 7% of orlistat recipients withdrew because of gastrointestinal-related adverse events (no further details provided).

• During phase III studies and subsequent follow up surveys, 11 cases of breast cancer were observed in women aged ≥45 years who received orlistat 120mg 3 times daily for up to 2 years compared with 3 cases with placebo. A concern regarding this imbalance was dismissed after re-evaluation of pre-existing clinical data and follow-up examinations.[33]

The tumours were assessed with respect to size, histological features and the presence of carcinoma and/or lymph node metastases.

- Seven independent experts (in the fields of histopathology, mammography and oncology) unanimously agreed that of these cases, 8 existed before study initiation and 1 case was a carcinoma *in situ*. The experts concluded that 3 and 2 cases, in the orlistat 120mg and placebo groups, respectively, were 'possibly emerging after treatment initiation'.[33] Thus there was no difference in the incidence of breast cancer between orlistat and placebo recipients (0.4 and 0.35% of the ≥45 year-old population; no cases were found in women aged <45 years).

- Furthermore, genotoxicity and carcinogenicity animal studies showed no evidence that orlistat could initiate or stimulate the growth of mammary or other tumours.[33] Systemic exposure to the drug in these studies was many times greater than that in humans.

- Thus, there is no evidence for a causal or stimulatory association between orlistat and breast cancer.[33]

5. Orlistat: Current Status

Orlistat is a gastrointestinal lipase inhibitor that is launched or approved in >15 countries in Europe, South America and Southeast Asia/Pacific. The drug was well tolerated when administered to obese patients for up to 2 years and resulted in a significant weight loss when given at a dosage of 120mg 3 times daily.

References

1. Obesity: advances in understanding and treatment. Drug Mark Dev 1995 May 22; 6: 26-41
2. Beales PL, Kopelman PG. Options for the management of obesity. PharmacoEconomics 1994; 5 Suppl. 1: 18-32
3. National Task Force on Obesity. Long-term pharmacotherapy in the management of obesity. JAMA 1996 Dec 18; 276 (23): 1907-15
4. Pisunyer. Guidelines for the approval and use of drugs to treat obesity – a position paper of the North American Association for the Study of Obesity. Obes Res 1995 Sep; 3: 473-8
5. Atkinson RL, Blank RC, Loper JF, et al. Combined drug treatment of obesity. Obes Res 1995 Nov; 3 Suppl. 4: 497-500
6. Borgstrom B. Mode of action of tetrahydrolipstatin: a derivative of the naturally occurring lipase inhibitor lipstatin [in English]. Biochim Biophys Acta 1988 Oct 14; 962: 308-16
7. Weibel EK, Hadvary P, Hochuli E, et al. Lipstatin, an inhibitor of pancreatic lipase, produced by Streptomyces toxytricini. I. Producing organism, fermentation, isolation and biological activity [in English]. J Antibiot Tokyo 1987 Aug; 40: 1081-5
8. Hadvary P, Lengsfeld H, Wolfer H. Inhibition of pancreatic lipase in vitro by the covalent inhibitor tetrahydrolipstatin [in English]. Biochem J 1988 Dec 1; 256: 357-61
9. Zhi J, Melia AT, Eggers H, et al. Review of limited systemic absorption of orlistat, a lipase inhibitor, in healthy human volunteers. J Clin Pharmacol 1995 Nov; 35: 1103-8
10. Hauptman JB, Jeunet FS, Hartmann D. Initial studies in humans with the novel gastrointestinal lipase inhibitor ro-18-0647 (tetrahydrolipstatin). Am J Clin Nutr 1992 Jan; 55 Suppl.: 309-13
11. Güzelhan G, Odink J, Niestijl JJ, et al. Influence of dietary composition on the inhibition of fat absorption by orlistat. J Int Med Res 1994 Sep-Oct; 22: 255-65
12. Hartmann D, Hussain Y, Güzelhan C, et al. Effect on dietary fat absorption of orlistat, administered at different times relative to meal intake. Br J Clin Pharmacol 1993 Sep; 36: 266-70
13. Tonstad S, Pometta D, Erkelens DW, et al. The effect of the gastrointestinal lipase inhibitor, orlistat, on serum lipids and lipoproteins in patients with primary hyperlipidaemia. Eur J Clin Pharmacol 1994; 46 (5): 405-10
14. Reitsma JB, Cabezas MC, Debruin TWA, et al. Relationship between improved postprandial lipemia and low-density lipoprotein metabolism during treatment with tetrahydrolipstatin, a pancreatic lipase inhibitor. Metabolism 1994 Mar; 43: 293-8
15. Drent ML, Larsson I, Williamolsson T, et al. Orlistat (RO 18-0647), a lipase inhibitor, in the treatment of human obesity: a multiple dose study. Int J Obes 1995 Apr; 19: 221-6
16. Lucas C. A 2-year placebo-controlled study of orlistat in the treatment of obesity [abstract no. 0339]. Diabetes 1997 May; 46 Suppl. 1: 86A
17. Rissanen A. Long-term weight management in obesity with orlistat, a new gastrointestinal lipase inhibitor [abstract no. 0342]. Diabetes 1997 May; 46 Suppl. 1: 87A
18. Noack R. Two-year study of orlistat in the treatment of obesity [abstract]. 79th Annual meeting of the American Endocrine Society (June 1997)
19. Drent ML, Popp-Snijders C, Ader HJ, et al. Lipase inhibition and hormonal status, body composition and gastrointestinal processing of a liquid high-fat mixed meal in moderately obese subjects [in English]. Obes Res 1995 Nov; 3: 573-81
20. Froehlich F, Hartmann D, Guezelhan C, et al. Influence of orlistat on the regulation of gallbladder contraction in man: a randomized double-blind placebo-controlled crossover study. Dig Dis Sci 1996 Dec; 41: 2404-8
21. Melia AT, Zhi J, Koss-Twardy SG, et al. The influence of reduced dietary fat absorption induced by orlistat on the pharmacokinetics of digoxin in healthy volunteers. J Clin Pharmacol 1995 Aug; 35: 840-3
22. Melia AT, Mulligan TE, Zhi J. Lack of effect of orlistat on the bioavailability of a single dose of nifedipine extended-release tablets (Procardia XL) in healthy volunteers. J Clin Pharmacol 1996 Apr; 36: 352-5
23. Melia AT, Mulligan TE, Zhi J. The effect of orlistat on the pharmacokinetics of phenytoin in healthy volunteers. J Clin Pharmacol 1996 Jul; 36: 654-8

24. Zhi J, Melia AT, Koss-Twardy SG, et al. The influence of orlistat on the pharmacokinetics and pharmacodynamics of glyburide in healthy volunteers. J Clin Pharmacol 1995 May; 35: 521-5
25. Zhi J, Melia AT, Guerciolini R, et al. The effect of tetrahydrolipstatin on the pharmacokinetics and pharmacodynamics of warfarin in healthy volunteers. J Clin Pharmacol 1996 Jul; 36: 659-66
26. Weber C, Tam YK, Schmidtke-Schrezenmeier G. Effect of the lipase inhibitor orlistat on the pharmacokinetics of four different antihypertensive drugs in healthy volunteers. Eur J Clin Pharmacol 1996 Sep; 51: 87-90
27. Hartmann D, Güzelhan C, Zuiderwijk PBM. Lack of interaction between orlistat and oral contraceptives. Eur J Clin Pharmacol 1996 Jul; 50: 421-4
28. Melia AT, Koss-Twardy SG, Zhi J. The effect of orlistat, an inhibitor of dietary fat absorption, on the absorption of vitamins A and E in healthy volunteers. J Clin Pharmacol 1996 Jul; 36: 647-53
29. Zhi J, Melia AT, Koss-Twardy SG, et al. The effect of orlistat, an inhibitor of dietary fat absorption, on the pharmacokinetics of beta-carotene in healthy volunteers. J Clin Pharmacol 1996 Feb; 36: 152-9
30. Canovatchel W. Long-term tolerability profile of orlistat, an intestinal lipase inhibitor [abstract]. F. Hoffmann-La Roche (New Jersey). 1997 (Data on file). Presented at the 16th IDF Congress, Helsinki, 1997
31. Van Gaal LF, Broom JI, Enzi G, et al. Efficacy and tolerability of orlistat in the treatment of obesity: a 6-month dose-ranging study. Eur J Pharmacol 1998; 54: 125-32
32. Hollander P. A 57-week study of orlistat in the treatment of obese patients with NIDDM [abstract no. 0213]. Diabetes 1997 May; 46 Suppl. 1: 55A
33. Roche 1998. Xenical® (orlistat) Advisory Committee briefing document. Presented at the Advisory Committee. 1998 Mar 13

Correspondence: *Wendy McNeely*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz