REVIEW ARTICLE

Drug Safety 2008; 31 (1): 53-65
0114-5916/08/0001-0053/$48.00/0

Orlistat-Associated Adverse Effects and Drug Interactions

A Critical Review

Theodosios D. Filippatos,[1] *Christos S. Derdemezis*,[1] *Irene F. Gazi*,[1] *Eleni S. Nakou*,[1] *Dimitri P. Mikhailidis*[2] and *Moses S. Elisaf*[1]

1 Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece
2 Department of Clinical Biochemistry (Vascular Disease Prevention Clinics), Royal Free Hospital, London, UK

Contents

Abstract

Orlistat, an anti-obesity drug, is a potent and specific inhibitor of intestinal lipases. In light of the recent US FDA approval of the over-the-counter sale of orlistat (60 mg three times daily), clinicians need to be aware that its use may be associated with less well known, but sometimes clinically relevant, adverse effects. More specifically, the use of orlistat has been associated with several mild-to-moderate gastrointestinal adverse effects, such as oily stools, diarrhoea, abdominal pain and faecal spotting. A few cases of serious hepatic adverse effects (cholelithiasis, cholostatic hepatitis and subacute liver failure) have been reported.

However, the effects of orlistat on non-alcoholic fatty liver disease are beneficial. Orlistat-induced weight loss seems to have beneficial effects on blood pressure. No effect has been observed on calcium, phosphorus, magnesium, iron, copper or zinc balance or on bone biomarkers. Interestingly, the use of orlistat has been associated with rare cases of acute kidney injury, possibly due to the increased fat malabsorption resulting from the inhibition of pancreatic and gastric lipase by orlistat, leading to the formation of soaps with calcium and resulting in increased free oxalate absorption and enteric hyperoxaluria. Orlistat has a beneficial effect on carbohydrate metabolism. No significant effect on cancer risk has been reported with orlistat.

Orlistat interferes with the absorption of many drugs (such as warfarin, amiodarone, ciclosporin and thyroxine as well as fat-soluble vitamins), affecting their bioavailability and effectiveness.

This review considers orlistat-related adverse effects and drug interactions. The clinical relevance and pathogenesis of these effects is also discussed.

Orlistat is an anti-obesity drug indicated at a dose of 120 mg three times daily, and in conjunction with a mild hypocaloric diet, for the treatment of obese patients (body mass index [BMI] ≥30 kg/m^2), and overweight patients (BMI ≥28 kg/m^2) with associated risk factors.[1] The drug is a potent and specific inhibitor of intestinal lipases: in healthy volunteers, it achieves 46.6–91.4% inhibition of gastric lipase and 51.2–81.6% inhibition of pancreatic lipase[2] and has little or no activity against amylase, trypsin, chymotrypsin and phospholipases.[3] Intestinal lipases breakdown dietary triglycerides into fatty acids and monoglycerides, which are then absorbed. The mean maximum percentage of ingested fat excreted in the faeces is approximately 32% during orlistat administration compared with 5% during administration of placebo.[4] Orlistat works within the gut and is minimally absorbed into the systemic circulation:[5] the results of five key double-blind, placebo-controlled phase II/III studies suggested that systemic exposure of orlistat is negligible and, at a clinically efficacious dose level, orlistat is unlikely to produce systemic lipase inhibition.[6,7] However, in these studies, there was sporadic detection of intact orlistat in plasma, although measurable concentrations were low (<10 ng/mL or 0.02 μmol/L) and there was no evidence of accumulation.[7]

Obesity is a problem of increasing concern worldwide, resulting in a significant rise in the number of prescriptions for anti-obesity drugs. As the US FDA has recently approved the over-the-counter sale of orlistat (at a low dosage of 60 mg three times daily),[8] clinicians need to be aware that its use may be associated with less well known, but sometimes clinically relevant adverse effects. Moreover, orlistat interferes with the absorption of many drugs, affecting their bioavailability and effectiveness.

This review considers these adverse effects and drug interactions.

We searched MEDLINE (up to February 2007) using combinations of the following key words: 'orlistat', 'adverse effects', 'side effects', 'liver', 'muscle', 'hepatotoxicity', 'gastrointestinal', 'skin', 'eye', 'central nervous system', 'pancreatitis', 'autoimmune disorders', 'arthritis', 'headache', 'cancer', 'renal disease' and 'drug interactions'. We also conducted a manual search of major randomized clinical trials with orlistat. Moreover, we scrutinized the reference lists from original papers, case reports and review articles as well as major randomized clinical trials with orlistat.

1. Adverse Effects

A summary of the adverse effects of olistat is given in table I.

Table I. Reported orlistat-associated adverse effects

Body system	Adverse effects
Gastrointestinal system	Fatty/oily stool, faecal urgency, diarrhoea, flatulence, abdominal pain, faecal spotting, anal fissure, cholelithiasis, pancreatitis, acute cholestatic hepatitis, subacute liver failure, massive hepatocellular necrosis, severe hepatic injury
Blood pressure	Hypertension (17 cases)
Nervous system	Depression, malaise, lassitude, headache, forgetfulness
Renal function	Enteric hyperoxaluria, acute kidney injury secondary to acute oxalate nephropathy, rapidly progressive renal failure, constipation, polyuria, polydipsia, lower-leg oedema
Endocrine system	Diabetic ketoacidosis
Skin	Cutaneous vasculitis, lichenoid eruption
Genitalia	Vaginitis, vulvitis

1.1 Gastrointestinal System

Orlistat, as is expected as a result of its mechanism of action, is associated with gastrointestinal (GI) adverse effects: fatty/oily stools, faecal urgency, diarrhoea, flatulence, abdominal pain, faecal spotting and anal fissures have all been reported.[9-19] In randomized controlled trials, the GI adverse effects have been significantly more common in the orlistat groups compared with the placebo groups.[10-14,16,17] A meta-analysis of studies in obese patients receiving orlistat at a dosage of 120 mg three times daily (2038 patients) showed an increase in mild-to-moderate adverse GI effects compared with placebo (1740 patients).[20] However, complaints of mild to moderately severe GI adverse effects generally decreased in frequency with ongoing orlistat treatment.[21]

Cholelithiasis has been reported in patients taking orlistat, but there is no evidence that this adverse effect is more common with orlistat use compared with placebo.[9,22] Orlistat does not appear to be associated with decreased postprandial gallbladder contraction.[23] However, there have been at least 99 reports of pancreatitis associated with the use of this drug.[22] Cholelithiasis and increased alcohol consumption by obese subjects seem to be the most obvious links between orlistat and pancreatitis. However, orlistat was reported to be associated with acute pancreatitis with normal amylase in one male patient who had no evidence of biliary disease and was abstinent from alcohol.[22] It must be stated that placebo-controlled trials involving patients treated with orlistat for ≥2 years showed no increase in the incidence of pancreatitis.[10,13,24]

Orlistat has been associated with serious hepatic adverse events in a few cases: one case of acute cholostatic hepatitis has been reported with the use of the drug,[25] and there have been two reports of orlistat-associated subacute liver failure[26,27] for which orthotopic liver transplantation was required. In one of these cases the liver showed submassive hepatocellular necrosis.[27] Massive hepatocellular necrosis has also been reported in another case,[28] but this may represent a rare idiosyncratic event associated with the use of the drug. Furthermore, orlistat has been reported to cause severe hepatic injury in a 15-year-old Thai female.[29] In this patient, the presence of low-grade fever, eosinophilia, elevated immunoglobulin-E levels and cytopenia indicated an immunoallergic reaction.

Orlistat has, however, beneficial effects on non-alcoholic fatty liver disease (NAFLD), a common cause of liver dysfunction, with a prevalence ranging between 10% and 51% in the general population.[30,31] Several studies have shown that orlistat use was associated with decreased serum activity of aminotransferases and/or a reversal of steatosis in liver ultrasound images.[30,32,33]

Of note, there is evidence that the GI adverse effects of orlistat may not only be due to lipase inhibition. In Wistar rats, orlistat caused histological damage in brush border membranes and connective tissues of the villi of the small intestinal mucosa.[34] The drug also induced an increased lymphocyte migration to the mucosa of the small intestine. This damage was partially prevented by dexamethasone.[34] However, these effects have not been replicated in human studies.

Orlistat accelerates gastric emptying and diminishes the incretin response to a high-fat meal, effects that may result in the exacerbation of postprandial glycaemia.[35,36] However, orlistat does not influence physiological and behavioural measures of ap-

petite in response to high-fat meals.[37] Moreover, the drug does not significantly alter the plasma cholecystokinin concentrations during a high-fat meal.[37]

Orlistat treatment has no direct effect on anorectal function or continence.[38] Faecal spotting occurs during treatment with orlistat when patients with subclinical anorectal dysfunction are exposed to the effects of orlistat on the stool (increased stool volume and altered stool composition).[38]

Olestra (an artificial fat substance) has added GI adverse effects when concomitantly used with orlistat, an effect that may lead to premature discontinuation of the anti-obesity therapy.[39] Of note, it has been reported that the GI adverse effects of orlistat may be prevented by the concomitant intake of natural fibre, such as psyllium mucilloid.[40] Loperamide has also shown beneficial effects on stool consistency and continence in obese subjects taking orlistat.[41]

There are cases where the use of orlistat has been beneficial due to its GI effects. In three cases, orlistat administration provided relief of intractable constipation in obese, chronic-pain patients with opioid-induced constipation.[42]

1.2 Blood Pressure and Heart Rate

There are no reports of orlistat-associated cardiac arrhythmias in the literature. A meta-analysis showed that treatment for 1 year with orlistat is associated with a mild but significant decrease in heart rate in obese subjects with uncontrolled hypertension.[43] However, other trials did not show any significant change in heart rate during orlistat treatment.[44,45]

In randomized clinical trials, weight loss with orlistat was associated with a beneficial effect on blood pressure.[46,47] The beneficial effect of orlistat on blood pressure has been established in healthy obese subjects,[48] in hypertensive patients,[43-45] in patients with the metabolic syndrome[12,49-52] and in patients with diabetes mellitus.[11,12,53,54] Most trials showed that the beneficial effect of orlistat on blood pressure was greater compared with that of placebo;[10,12,13,43,45,55-58] however, in one trial in Chinese subjects, no difference was observed.[59] The divergence in the blood pressure effect between the orlistat and placebo groups observed in most trials may be attributed to significant differences in weight loss. However, orlistat seems to be more beneficial than another anti-obesity drug, sibutramine, as far as blood pressure control is concerned.[60,61]

These data notwithstanding, there are at least 17 case reports of orlistat-associated hypertension.[62-64] In the majority of the cases reported, information on blood pressure measurements and follow-up were limited. The mechanism for this reaction is not clear, but fluid retention is a possibility.[62]

1.3 Nervous System

A variety of drugs used to assist with weight loss have been implicated in the precipitation or induction of depressive symptoms and disorders.[65] Orlistat has been associated with depression in one case;[66] however, there is, as yet, no substantial link between orlistat and major depression.[65]

Obese patients very often have increased depression scores. Several studies have shown an improvement of these scores after weight loss.[65] In a recent study, we investigated the effects of orlistat on mood in obese healthy women.[67] We observed a significant improvement in mood after weight loss with orlistat, although this effect was not significantly greater when compared with diet alone.[67] Furthermore, orlistat has been shown to lead to greater weight loss and to a greater reduction in the number of binge episodes in patients with binge-eating disorder.[68] The drug has also been beneficial in a schizophrenic patient who exhibited substantial weight gain during antipsychotic therapy.[69] The use of orlistat as a purging substance by two individuals with bulimia has been reported.[70]

Finally, orlistat has been reported to cause malaise, lassitude, headache or forgetfulness in a few cases.[71,72]

1.4 Musculoskeletal System

Weight loss has been associated with increased risk of osteoporosis and bone demineralisation.[73] Theoretically, the inhibition of dietary fat absorption subsequent to inhibition of intestinal lipase activity

by orlistat may have an adverse effect on dietary mineral absorption and balance due to the formation of insoluble mineral soaps within the intestine. However, in two studies, orlistat administration for 21 days had no significant effect on calcium, phosphorus, magnesium, iron, copper or zinc balance.[74,75] In addition, biomarkers of bone turnover, as well as serum and urine electrolytes, were not affected by orlistat.[74] Another study reported that 1 year of treatment with orlistat induced a relative increase in bone turnover in favour of resorption, possibly due to malabsorption of vitamin D and/or calcium.[76] However, no changes in bone mass or density were seen after 1 year of orlistat treatment apart from those explained by the weight loss itself. Thus, orlistat treatment seems safe from a 'bone preserving' point of view. Of note, in the same study, Gotfredsen et al.[76] suggested that a vitamin D and calcium supplement should be taken during treatment with orlistat. However, this suggestion was not verified in the XENDOS (XENical in the prevention of Diabetes in Obese Subjects) study[10] because there was no significant decrease in 1,25-hydroxyvitamin D during the 4-year orlistat treatment.

1.5 Renal Function

It is known that unabsorbed fat may react with calcium in the intestinal lumen, limiting the amount of free calcium able to bind with oxalate. These reactions result in an increase of intestinal oxalate absorption leading to enteric hyperoxaluria.[77] In an experimental rat model, the use of orlistat, especially in conjunction with a diet rich in oxalate alone or associated with fat, led to significant oxalate absorption and a marked increase in urinary oxalate. This finding was accompanied by a slight reduction in urinary calcium and urinary magnesium, therefore elevating the risk of kidney stone formation.[77] Recently, Singh et al.[78] reported a case of orlistat-induced acute kidney injury secondary to acute oxalate nephropathy in a Caucasian woman with underlying chronic kidney disease (CKD). A kidney biopsy revealed the deposition of calcium oxalate crystals within tubular lumens. The likely scenario in this case was that increased fat malabsorption resulting from the inhibition of pancreatic and gastric lipase by orlistat led to the formation of soaps with calcium, resulting in increased free oxalate absorption and to enteric hyperoxaluria. In addition, the combination of underlying CKD and mild volume depletion from the drug-induced steatorrhoea is likely to have further increased the risk of calcium oxalate crystal precipitation within renal tubules.[78] Similarly, a case of acute on chronic renal failure was recently reported in a 55-year-old diabetic woman with CKD.[79] The rapidity of the deterioration in renal function could not be explained by the patient's diabetic status, suggesting the intrarenal precipitation of calcium oxalate due to orlistat as a possible cause.

Constipation, polyuria, polydypsia and lower-leg oedema has been reported with orlistat use in a 42-year-old Caucasian woman.[80] Pedal oedema has also been reported.[80] Nevertheless, there is no evidence of causal association between these adverse effects and orlistat treatment.

1.6 Endocrine System

Orlistat improves carbohydrate metabolism both in obese otherwise healthy subjects[21] and in obese diabetic patients.[81,82] The drug also has beneficial effects on the dose requirements of antidiabetic drugs or insulin.[54,59,83,84] Although orlistat is not recommended for use in pregnancy or when nursing,[85] the drug has been shown to improve endothelial function in women with previous gestational diabetes.[86] Of interest is that the improvement of endothelial function was associated with the lowering of levels of low-density lipoprotein cholesterol by orlistat, but not with weight loss *per se*.[86] Moreover, orlistat decreases elevated serum levels of advanced glycation end-products (AGEs) in women with polycystic ovary syndrome (PCOS), independently of BMI changes.[87] In addition to orlistat-induced improvement in insulin resistance, which influences the formation and clearance of AGEs, there are data that indicate that AGEs are absorbed from exogenous sources and that fat has a greater effect on the absorption of these food glycotoxins

than do proteins and carbohydrates.[87,88] Therefore, the decrease of fat absorption induced by orlistat leads to decreased absorption of AGEs.[88]

Furthermore, orlistat improves leptinaemia, but increases serum neuropeptide Y levels observed in obese subjects.[89] In turn, leptin may exert several effects on various systems including the vasculature.[90] Orlistat reduces testosterone concentration in women with PCOS.[91] Orlistat also increases the postprandial levels of glucagon-like peptide 1, which leads to reduced food intake, an effect that may contribute to the weight loss associated with the use of this drug.[92]

Orlistat has been associated with diabetic ketoacidosis in a Caucasian woman with type 1 diabetes.[93] In this patient, orlistat administration seemed to have caused progressive dehydration and a decrease in intravascular volume, probably secondary to watery stools. Initially, this led to insulin resistance and increased insulin requirements, followed by diabetic ketoacidosis. Thus, patients with type 1 diabetes need close monitoring when given orlistat for obesity management.[93]

1.7 Skin

Orlistat has been associated with cutaneous vasculitis:[94] in one report, a 34-year-old woman experienced myalgia, arthralgia and palpable purpura, mainly involving the lower extremities, 72 hours after the initiation of orlistat treatment. A skin biopsy revealed a leukocytoclastic vasculitis affecting capillaries and venules. A rapid improvement of the cutaneous lesions was achieved after the discontinuation of the drug and prescription of NSAIDS.[94]

Orlistat was also associated with lichenoid eruption in the vulva, feet and axillae in a 42-year-old woman.[95] In this case, the temporal relationship between starting orlistat treatment and the onset of rash, the rapid response to withdrawal from the drug, and the pathology supportive of a lichenoid drug eruption suggest that orlistat was the cause of the skin lesions.

Of note, the Medicines and Healthcare Products Regulatory Agency and The Committee on Safety of Medicines in the United Kingdom received reports of 1519 reactions related to orlistat between September 1998 and February 2005, of which 182 (11.8%) were for skin and subcutaneous tissue disorders.[95] However, in large placebo-controlled trials, there was no evidence of increased skin- or subcutaneous tissue-related adverse effects with orlistat treatment compared with placebo.[10,11,13,24]

1.8 Genitalia

Vaginitis and vulvitis have been reported in patients receiving orlistat; however, no causal association could be established.[72]

1.9 Cancer

Studies in animals suggest that a high intake of dietary fat is associated with a higher prevalence of colorectal cancer.[96,97] This increased prevalence may be at least partially related to intracolonic changes caused by the direct action of fat on colonocytes.[98] Garcia et al.[99] investigated the effects of orlistat on the formation of colonic aberrant crypt foci and cell proliferation in Wistar rats that had received the carcinogen dimethyl-hydrazine. Orlistat was associated with a significant increase in the number of colonic aberrant crypt foci and cell proliferation in these animals, which was independent of the high-fat diet consumed. It must be noted that in long-term studies (duration 2–4 years), such as the XENDOS study,[10] no significant increase was observed in any type of cancer with orlistat treatment compared with placebo.

Of note, during the last few years a new molecular target and a potential new application for orlistat have been investigated. Orlistat is a novel inhibitor of the thioesterase domain of fatty acid synthase (Fas), an enzyme strongly linked to tumour progression.[100,101] The drug has been shown to inhibit endothelial cell proliferation and angiogenesis, through the inhibition of Fas activity.[102] By virtue of its ability to inhibit Fas, orlistat induces tumour cell apoptosis, and inhibits the growth of prostate cancer in nude mice.[100] Orlistat has also exhibited antitumoral actions in ovarian cancer cells[103] and breast cancer cells.[104] Fas is up-regulated in about 50% of breast cancers and is an indicator of poor

prognosis. These findings reveal that the development of orlistat formulations with greater bioavailability targeting the lipogenic activity of Fas may open a novel therapeutic avenue in the treatment of prostate or breast carcinomas.[105]

2. Drug Interactions

A summary of the interactions of orlistat with other drugs is given in table II.

2.1 Fat-Soluble Vitamins

The absorption of fat-soluble vitamins may be decreased by orlistat. In healthy volunteers, the short-term use of orlistat significantly reduced the absorption of betacarotene and vitamin E, but not vitamin A.[106,107] During 2-year clinical studies,[13,17] plasma concentrations of fat soluble vitamins (A, D, E and betacarotene) decreased among subjects taking orlistat, but generally remained within the clinical reference range. In the XENDOS study,[10] there were statistically significant decreases in plasma concentrations for all assessed fat-soluble vitamins, with the exception of 1,25-hydroxyvitamin D, in the orlistat group compared with the placebo group after 4 years of treatment. However, the mean level of each assessed vitamin remained well within its reference range at all times during the 4-year study for both the orlistat and the placebo groups. Obese adolescents receiving orlistat, although being prescribed a multivitamin supplement, experienced significantly decreased absorption of vitamin E and serum vitamin D levels compared with baseline levels.[108] It may be prudent to at least monitor vitamin D concentrations in adolescents who take orlistat. Finally, 3-month therapy with orlistat does not affect the serum levels of vitamin B12 and folic acid.[109]

Table II. Drug-drug interactions with orlistat

Drugs reported to interfere with orlistat
Fat-soluble vitamins, warfarin, amiodarone, ciclosporin, lamotrigine, valproic acid, vigabatrin, gabapentin, thyroxine
Drugs not (reported as) interfering with orlistat
Phenytoin, fluoxetine, amitriptyline, metformin, phentermine, sibutramine, digoxin, losartan, atenolol, furosemide, captopril, nifedipine, pravastatin, simvastatin, atorvastatin, haloperidol, clozapine, clomipramine, desipramine, carbamazepine

2.2 Warfarin

In a short-term study by Zhi et al.,[110] orlistat did not result in any change in warfarin pharmacokinetics or pharmacodynamics. However, a case of increased International Normalised Ratio (INR) associated with the addition of orlistat has been reported in a 66-year-old patient with a history of atrial fibrillation receiving warfarin therapy.[111] The introduction of orlistat may reduce the absorption of fat-soluble vitamin K, possibly resulting in a lowering of warfarin dose requirements. This may be partly due to a shift to a lower fat diet with decreased amounts of vitamin K and/or to an effect on vitamin K absorption.[111] Because of a potential decrease in vitamin K absorption, patients stabilized on warfarin should be closely monitored for changes in coagulation parameters.[21]

2.3 Amiodarone

Amiodarone is one of the most frequently prescribed antiarrhythmic drugs in the US. Orlistat has been associated with decreased absorption of this lipophilic drug, a finding which may be clinically relevant:[112] the potential interaction between orlistat and amiodarone may lead to sub-therapeutic levels of amiodarone.

2.4 Ciclosporin

There are several reports suggesting that orlistat interferes with the absorption of ciclosporin (cyclosporine).[113-121] This interference is of clinical importance because ciclosporin is used in transplant patients and the reduction of its plasma concentration may induce acute transplant rejection. In a 29-year-old woman, orlistat induced subtherapeutic plasma levels of ciclosporin, even though orlistat was administered 2 hours before the injection of ciclosporin and the dose of orlistat was decreased to only 240 mg/day.[117] This case suggests that the decreased plasma ciclosporin concentration is possibly due to reduced absorption of dietary fats and not to a drug-drug interaction.[117] Furthermore, the ad-

ministration of orlistat to a patient who does not follow a low-fat diet often results in diarrhoea, a factor that may also diminish the absorption of ciclosporin. Adherence to a low-fat diet should be strongly recommended if orlistat is prescribed to patients taking ciclosporin. Moreover, strict monitoring of the plasma levels of ciclosporin is important.[117]

2.5 CNS Agents

Weight gain is a commonly reported adverse effect of antiepileptic drugs. It has been reported that orlistat reduced the absorption of lamotrigine in an 18-year-old epileptic woman, who experienced an increased frequency of seizures.[122] By reducing the dietary absorption of fat, orlistat can potentially alter the absorption of lipophilic drugs, and lamotrigine is considered to be highly lipophilic.[122] Patients who receive lamotrigine (and possibly other lipophilic antiepileptic medications, such as valproic acid, vigabatrin and gabapentin) and orlistat for weight control need close monitoring, because alterations in drug serum concentrations can lead to deterioration in epileptic control.[122]

Similarly, long-term psychopharmacotherapy induces weight gain, which is a major problem affecting compliance and long-term outcomes. Orlistat does not induce any clinically relevant changes in plasma concentrations of haloperidol, clozapine, clomipramine, desipramine or carbamazepine over an 8-week period.[123] Therefore, orlistat may be used during long-term pharmacotherapy in overweight and obese psychiatric patients. In addition, orlistat was beneficial in the treatment of clozapine-induced hyperglycaemia and weight gain in a 35-year-old man with chronic schizophrenia.[124]

2.6 Oral Contraceptives

A report suggested caution with the concomitant use of orlistat and oral contraceptives.[125] However, a placebo-controlled, double-blind study concluded that orlistat does not influence the ovulation-suppressing action of oral contraceptives.[126]

2.7 Thyroxine

Orlistat has been reported to induce symptomatic hypothyroidism in a patient with papillary carcinoma of the thyroid, who was receiving thyroxine as suppressive treatment.[127] Thyroxine absorption is influenced by the content of the GI tract. Some substances bind to thyroxine, making it unavailable for diffusion across the gut wall. Orlistat may also bind to thyroxine and prevent its absorption from the small intestine. Clinicians should be aware of this potential interference of this drug with thyroxine absorption.[127]

2.8 Alcohol

In healthy men, lipase inhibition with orlistat accelerates gastric emptying of alcohol-containing drinks, which is associated with an initially greater blood-alcohol response. However, this effect is relatively modest and unlikely to be of clinical significance.[128] Another study in healthy volunteers showed no significant influence of orlistat on ethanol pharmacokinetics.[129] In any case, alcohol consumption during a weight-loss programme should be limited to one or two alcoholic drinks per week, preferably with meals, irrespective of orlistat use.

2.9 Antidiabetic Agents

Orlistat has been beneficially used, in combination with insulin[81,130] or oral antidiabetic drugs,[54,59,83,84,131,132] in type 2 diabetic patients. Orlistat does not significantly alter the pharmacokinetics of glibenclamide (glyburide),[133] or metformin.[119] However, there is evidence that the combination of orlistat with sulfonylureas or metformin causes increased episodes of mild to moderate hypoglycaemia compared with placebo in diabetic patients.[84] Furthermore, in the study by Kelley et al.[130] in overweight and obese patients with insulin-treated type 2 diabetes, episodes of hypoglycaemia occurred in a greater proportion of orlistat-treated than placebo-treated patients (16.9% and 9.7%, respectively, $p < 0.05$). In the majority of patients, hypoglycaemic symptoms were mild to moderate. Only four patients (one in the placebo group and

three in the orlistat group) required medical intervention because of hypoglycaemia.[130] Clinicians should monitor glucose plasma levels in diabetic patients on orlistat in order to adjust the dose of insulin or oral antidiabetic drugs.

2.10 Other Drugs

Orlistat had no significant effect on the pharmacokinetics of phenytoin,[134] fluoxetine,[112] amitriptyline,[119] phentermine,[119] sibutramine,[119] digoxin,[3] losartan,[119] atenolol,[135] furosemide,[135] captopril,[135] nifedipine,[135,136] pravastatin,[3] simvastatin[112] or atorvastatin.[119]

Of note, orlistat has added beneficial effects on metabolic parameters when co-administered with statins[137] or fibrates[49,50] in overweight and obese patients with hypercholesterolaemia or metabolic syndrome.

3. Conclusions

Orlistat acts primarily locally in the GI tract to inhibit lipases, enzymes that are crucial for the digestion of long-chain triglycerides. The drug, in conjunction with a hypocaloric diet, is useful for the treatment of obesity. The benefit-risk profile of orlistat appears positive. Orlistat administration has been associated mainly with GI adverse events. These GI-related adverse events are generally decreased in frequency with ongoing orlistat treatment. However, large randomized clinical trials testing anti-obesity drugs have very high drop-out rates, probably as a result of the difficulty obese patients have in following hypocaloric diets over the long term or to the fact that patients intolerant to orlistat have to withdraw. In any case, the very high drop-out rate renders it difficult to determine which, if any, major adverse effects are associated with the drug over the long term.

Systemic adverse effects have rarely been reported with orlistat, and furthermore, many of the systemic adverse effects that have been associated with orlistat have not been reported in clinical trials, but in reports of weaker validity, such as case reports. Moreover, a causal relationship between statin use and these adverse effects has not been proven. Orlistat is used worldwide and has been extensively studied in many large clinical trials. However, with increasing use, some rare adverse effects may arise. Physicians should be vigilant in recognizing such adverse effects and report them to regulatory authorities, in order to make the widespread use of orlistat even safer.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. Some of the authors have given talks, attended conferences and participated in trials and advisory boards sponsored by various pharmaceutical companies including Roche.

References

1. Dahlin A, Beermann B. Incorrect use of orlistat and sibutramine in clinical practice. Eur J Clin Pharmacol 2007 Feb; 63 (2): 205-9
2. Carriere F, Renou C, Ransac S, et al. Inhibition of gastrointestinal lipolysis by Orlistat during digestion of test meals in healthy volunteers. Am J Physiol Gastrointest Liver Physiol 2001 Jul; 281 (1): G16-28
3. Guerciolini R. Mode of action of orlistat. Int J Obes Relat Metab Disord 1997 Jun; 21 Suppl. 3: S12-23
4. Zhi J, Melia AT, Guerciolini R, et al. Retrospective population-based analysis of the dose-response (fecal fat excretion) relationship of orlistat in normal and obese volunteers. Clin Pharmacol Ther 1994 Jul; 56 (1): 82-5
5. 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 (11): 1103-8
6. Zhi J, Melia AT, Funk C, et al. Metabolic profiles of minimally absorbed orlistat in obese/overweight volunteers. J Clin Pharmacol 1996 Nov; 36 (11): 1006-11
7. Zhi J, Mulligan TE, Hauptman JB. Long-term systemic exposure of orlistat, a lipase inhibitor, and its metabolites in obese patients. J Clin Pharmacol 1999 Jan; 39 (1): 41-6
8. US Food and Drug Administration. FDA approves orlistat for over-the-counter use [online]. Available from URL: http://www.fda.gov/bbs/topics/NEWS/2007/new01557.html [Accessed 2007 Oct 15]
9. Toplak H, Ziegler O, Keller U, et al. X-PERT: weight reduction with orlistat in obese subjects receiving a mildly or moderately reduced-energy diet: early response to treatment predicts weight maintenance. Diabetes Obes Metab 2005 Nov; 7 (6): 699-708
10. Torgerson JS, Hauptman J, Boldrin MN, et al. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care 2004 Jan; 27 (1): 155-61
11. Hanefeld M, Sachse G. The effects of orlistat on body weight and glycaemic control in overweight patients with type 2 diabetes: a randomized, placebo-controlled trial. Diabetes Obes Metab 2002 Nov; 4 (6): 415-23
12. Didangelos TP, Thanopoulou AK, Bousboulas SH, et al. The ORLIstat and Cardiovascular risk profile in patients with meta-

bolic syndrome and type 2 DIAbetes (ORLICARDIA) Study. Curr Med Res Opin 2004 Sep; 20 (9): 1393-401
13. Davidson MH, Hauptman J, DiGirolamo M, et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. JAMA 1999 Jan 20; 281 (3): 235-42
14. Chanoine JP, Hampl S, Jensen C, et al. Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. JAMA 2005 Jun 15; 293 (23): 2873-83
15. O'Meara S, Riemsma R, Shirran L, et al. A systematic review of the clinical effectiveness of orlistat used for the management of obesity. Obes Rev 2004 Feb; 5 (1): 51-68
16. O'Meara S, Riemsma R, Shirran L, et al. A rapid and systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity. Health Technol Assess 2001; 5 (18): 1-81
17. Sjostrom L, Rissanen A, Andersen T, et al. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. Lancet 1998 Jul 18; 352 (9123): 167-72
18. 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. Orlistat Dose-Ranging Study Group. Eur J Clin Pharmacol 1998 Apr; 54 (2): 125-32
19. Padwal R, Li SK, Lau DC. Long-term pharmacotherapy for overweight and obesity: a systematic review and meta-analysis of randomized controlled trials. Int J Obes Relat Metab Disord 2003 Dec; 27 (12): 1437-46
20. Canovatchel W. Long-term tolerability profile of orlistat, an intestinal lipase inhibitor [abstract]. 16th International Diabetes Federation Congress; 1997 Jul 25-27, Helsinki
21. Kiortsis DN, Filippatos TD, Elisaf MS. The effects of orlistat on metabolic parameters and other cardiovascular risk factors. Diabetes Metab 2005 Feb; 31 (1): 15-22
22. Napier S, Thomas M. 36 year old man presenting with pancreatitis and a history of recent commencement of orlistat: case report. Nutr J 2006; 5: 19
23. 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 (12): 2404-8
24. Richelsen B, Tonstad S, Rossner S, et al. Effect of orlistat on weight regain and cardiovascular risk factors following a very-low-energy diet in abdominally obese patients: a 3-year randomized, placebo-controlled study. Diabetes Care 2007 Jan; 30 (1): 27-32
25. Kim DH, Lee EH, Hwang JC, et al. A case of acute cholestatic hepatitis associated with orlistat [in Korean] [abstract]. Taehan Kan Hakhoe Chi 2002 Sep; 8 (3): 317-20
26. Montero JL, Muntane J, Fraga E, et al. Orlistat associated subacute hepatic failure. J Hepatol 2001 Jan; 34 (1): 173
27. Thurairajah PH, Syn WK, Neil DA, et al. Orlistat (Xenical)-induced subacute liver failure. Eur J Gastroenterol Hepatol 2005 Dec; 17 (12): 1437-8
28. Lau G, Chan CL. Massive hepatocellular [correction of hepatocullular] necrosis: was it caused by orlistat? Med Sci Law 2002 Oct; 42 (4): 309-12
29. Umemura T, Ichijo T, Matsumoto A, et al. Severe hepatic injury caused by orlistat. Am J Med 2006 Aug; 119 (8): e7
30. Diakou MC, Liberopoulos EN, Mikhailidis DP, et al. Pharmacological treatment of non-alcoholic steatohepatitis: the current evidence. Scand J Gastroenterol 2007 Feb; 42 (2): 139-47
31. Athyros VG, Mikhailidis DP, Didangelos TP, et al. Effect of multifactorial treatment on non-alcoholic fatty liver disease in metabolic syndrome: a randomised study. Curr Med Res Opin 2006 May; 22 (5): 873-83
32. Harrison SA, Fincke C, Helinski D, et al. A pilot study of orlistat treatment in obese, non-alcoholic steatohepatitis patients. Aliment Pharmacol Ther 2004 Sep 15; 20 (6): 623-8
33. Zelber-Sagi S, Kessler A, Brazowsky E, et al. A double-blind randomized placebo-controlled trial of orlistat for the treatment of _yclosporine_ fatty liver disease. Clin Gastroenterol Hepatol 2006 May; 4 (5): 639-44
34. Caner M, Dogruman H, Taskin E, et al. Effects of orlistat and its relationship with nitric oxide in the small intestinal mucosa. Chin J Physiol 2005 Dec 31; 48 (4): 217-22
35. O'Donovan D, Horowitz M, Russo A, et al. Effects of lipase inhibition on gastric emptying of, and on the glycaemic, insulin and cardiovascular responses to, a high-fat/carbohydrate meal in type 2 diabetes. Diabetologia 2004 Dec; 47 (12): 2208-14
36. Pilichiewicz A, O'Donovan D, Feinle C, et al. Effect of lipase inhibition on gastric emptying of, and the glycemic and incretin responses to, an oil/aqueous drink in type 2 diabetes mellitus. J Clin Endocrinol Metab 2003 Aug; 88 (8): 3829-34
37. Goedecke JH, Barsdorf M, Beglinger C, et al. Effects of a lipase inhibitor (orlistat) on cholecystokinin and appetite in response to a high-fat meal. Int J Obes Relat Metab Disord 2003 Dec; 27 (12): 1479-85
38. Fox M, Thumshirn M, Menne D, et al. The pathophysiology of faecal spotting in obese subjects during treatment with orlistat. Aliment Pharmacol Ther 2004 Feb 1; 19 (3): 311-21
39. Heck AM, Calis KA, McDuffie JR, et al. Additive gastrointestinal effects with concomitant use of olestra and orlistat. Ann Pharmacother 2002 Jun; 36 (6): 1003-5
40. Cavaliere H, Floriano I, Medeiros-Neto G. Gastrointestinal side effects of orlistat may be prevented by concomitant prescription of natural fibers (psyllium mucilloid). Int J Obes Relat Metab Disord 2001 Jul; 25 (7): 1095-9
41. Fox M, Stutz B, Menne D, et al. The effects of loperamide on continence problems and anorectal function in obese subjects taking orlistat. Dig Dis Sci 2005 Sep; 50 (9): 1576-83
42. Guarino AH. Treatment of intractable constipation with orlistat: a report of three cases. Pain Med 2005 Jul-Aug; 6 (4): 327-8
43. Sharma AM, Golay A. Effect of orlistat-induced weight loss on blood pressure and heart rate in obese patients with hypertension. J Hypertens 2002 Sep; 20 (9): 1873-8
44. Derosa G, Cicero AF, Murdolo G, et al. Efficacy and safety comparative evaluation of orlistat and sibutramine treatment in hypertensive obese patients. Diabetes Obes Metab 2005 Jan; 7 (1): 47-55
45. Bakris G, Calhoun D, Egan B, et al. Orlistat improves blood pressure control in obese subjects with treated but inadequately controlled hypertension. J Hypertens 2002 Nov; 20 (11): 2257-67
46. Avenell A, Broom J, Brown TJ, et al. Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement. Health Technol Assess 2004 May; 8 (21): iii-iv, 1-182
47. Zavoral JH. Treatment with orlistat reduces cardiovascular risk in obese patients. J Hypertens. 1998 Dec; 16 (12 Pt 2): 2013-7
48. Schneider R, Golzman B, Turkot S, et al. Effect of weight loss on blood pressure, arterial compliance, and insulin resistance in normotensive obese subjects. Am J Med Sci 2005 Oct; 330 (4): 157-60

49. Filippatos TD, Gazi IF, Liberopoulos EN, et al. The effect of orlistat and fenofibrate, alone or in combination, on small dense LDL and lipoprotein-associated phospholipase A (2) in obese patients with metabolic syndrome. Atherosclerosis 2007; 193 (2): 428-37
50. Filippatos TD, Kiortsis DN, Liberopoulos EN, et al. Effect of orlistat, micronised fenofibrate and their combination on metabolic parameters in overweight and obese patients with the metabolic syndrome: the FenOrli study. Curr Med Res Opin 2005 Dec; 21 (12): 1997-2006
51. Zanella MT, Uehara MH, Ribeiro AB, et al. Orlistat and cardiovascular risk profile in hypertensive patients with metabolic syndrome: the ARCOS study. Arq Bras Endocrinol Metabol 2006 Apr; 50 (2): 368-76
52. Reaven G, Segal K, Hauptman J, et al. Effect of orlistat-assisted weight loss in decreasing coronary heart disease risk in patients with syndrome X. Am J Cardiol 2001 Apr 1; 87 (7): 827-31
53. Halpern A, Mancini MC, Suplicy H, et al. Latin-American trial of orlistat for weight loss and improvement in glycaemic profile in obese diabetic patients. Diabetes Obes Metab 2003 May; 5 (3): 180-8
54. Hollander PA, Elbein SC, Hirsch IB, et al. Role of orlistat in the treatment of obese patients with type 2 diabetes. A 1-year randomized double-blind study. Diabetes Care 1998 Aug; 21 (8): 1288-94
55. Broom I, Wilding J, Stott P, et al. Randomised trial of the effect of orlistat on body weight and cardiovascular disease risk profile in obese patients: UK Multimorbidity Study. Int J Clin Pract 2002 Sep; 56 (7): 494-9
56. Derosa G, Cicero AF, Murdolo G, et al. Comparison of metabolic effects of orlistat and sibutramine treatment in type 2 diabetic obese patients. Diabetes Nutr Metab 2004 Aug; 17 (4): 222-9
57. Bloch KV, Salles GF, Muxfeldt ES, et al. Orlistat in hypertensive overweight/obese patients: results of a randomized clinical trial. J Hypertens 2003 Nov; 21 (11): 2159-65
58. Tong PC, Lee ZS, Sea MM, et al. The effect of orlistat-induced weight loss, without concomitant hypocaloric diet, on cardiovascular risk factors and insulin sensitivity in young obese Chinese subjects with or without type 2 diabetes. Arch Intern Med 2002 Nov 25; 162 (21): 2428-35
59. Kuo CS, Pei D, Yao CY, et al. Effect of orlistat in overweight poorly controlled Chinese female type 2 diabetic patients: a randomised, double-blind, placebo-controlled study. Int J Clin Pract 2006 Aug; 60 (8): 906-10
60. Filippatos TD, Kiortsis DN, Liberopoulos EN, et al. A review of the metabolic effects of sibutramine. Curr Med Res Opin 2005 Mar; 21 (3): 457-68
61. Padwal RS, Majumdar SR. Drug treatments for obesity: orlistat, sibutramine, and rimonabant. Lancet 2007 Jan 6; 369 (9555): 71-7
62. Persson M, Vitols S, Yue QY. Orlistat associated with hypertension [letter]. BMJ 2000 Jul 8; 321 (7253): 87
63. Johnston GD. Orlistat associated with hypertension: digit preference lays conclusions about orlistat open to doubt [letter]. BMJ 2001 Jan 13; 322 (7278): 110
64. Huber MH. Orlistat associated with hypertension: Roche concludes that there is not evidence of a casual association. BMJ 2001 Jan 13; 322 (7278): 110-1
65. Patten SB. Major depressive episodes and diet pills. Expert Opin Pharmacother 2002 Oct; 3 (10): 1405-9
66. Benazzi F. Depression induced by orlistat (Xenical) [letter]. Can J Psychiatry 2000 Feb; 45 (1): 87
67. Kiortsis DN, Tsouli S, Filippatos TD, et al. Effects of sibutramine and orlistat on mood in obese and overweight subjects: a randomized study. Nutr Metab Cardiovasc Dis. In press
68. Golay A, Laurent-Jaccard A, Habicht F, et al. Effect of orlistat in obese patients with binge eating disorder. Obes Res 2005 Oct; 13 (10): 1701-8
69. heleritis CG, Papadimitriou GN, Papageorgiou CC, et al. Excessive weight gain after remission of depression in a schizophrenic patient treated with risperidone: case report. BMC Psychiatry 2006; 6: 37
70. Fernandez-Aranda F, Amor A, Jimenez-Murcia S, et al. Bulimia nervosa and misuse of orlistat: two case reports. Int J Eat Disord 2001 Dec; 30 (4): 458-61
71. Kaya A, Aydin N, Topsever P, et al. Efficacy of sibutramine, orlistat and combination therapy on short-term weight management in obese patients. Biomed Pharmacother 2004 Dec; 58 (10): 582-7
72. Acharya NV, Wilton LV, Shakir SA. Safety profile of orlistat: results of a prescription-event monitoring study. Int J Obes 2006; 30: 1645-52
73. Pritchard JE, Nowson CA, Wark JD. Bone loss accompanying diet-induced or exercise-induced weight loss: a randomised controlled study. Int J Obes Relat Metab Disord 1996 Jun; 20 (6): 513-20
74. Pace DG, Blotner S, Guerciolini R. Short-term orlistat treatment does not affect mineral balance and bone turnover in obese men. J Nutr 2001 Jun; 131 (6): 1694-9
75. Zhi J, Moore R, Kanitra L. The effect of short-term (21-day) orlistat treatment on the physiologic balance of six selected macrominerals and microminerals in obese adolescents. J Am Coll Nutr 2003 Oct; 22 (5): 357-62
76. Gotfredsen A, Westergren Hendel H, Andersen T. Influence of orlistat on bone turnover and body composition. Int J Obes Relat Metab Disord 2001 Aug; 25 (8): 1154-60
77. Ferraz RR, Tiselius HG, Heilberg IP. Fat malabsorption induced by gastrointestinal lipase inhibitor leads to an increase in urinary oxalate excretion. Kidney Int 2004 Aug; 66 (2): 676-82
78. Singh A, Sarkar SR, Gaber LW, et al. Acute oxalate nephropathy associated with orlistat, a gastrointestinal lipase inhibitor. Am J Kidney Dis 2007 Jan; 49 (1): 153-7
79. Courtney AE, O'Rourke DM, Maxwell AP. Rapidly progressive renal failure associated with successful pharmacotherapy for obesity. Nephrol Dial Transplant 2007 Feb; 22 (2): 621-3
80. Packard KA, Wurdeman RL, Reyes AP. Constipation, polyuria, polydipsia, and edema associated with orlistat. Ann Pharmacother 2002 Jul-Aug; 36 (7-8): 1168-70
81. Rowe R, Cowx M, Poole C, et al. The effects of orlistat in patients with diabetes: improvement in glycaemic control and weight loss. Curr Med Res Opin 2005 Nov; 21 (11): 1885-90
82. Liberopoulos EN, Tsouli S, Mikhailidis DP, et al. Preventing type 2 diabetes in high risk patients: an overview of lifestyle and pharmacological measures. Curr Drug Targets 2006 Feb; 7 (2): 211-28
83. Berne C. A randomized study of orlistat in combination with a weight management programme in obese patients with type 2 diabetes treated with metformin. Diabet Med 2005 May; 22 (5): 612-8
84. Miles JM, Leiter L, Hollander P, et al. Effect of orlistat in overweight and obese patients with type 2 diabetes treated with metformin. Diabetes Care 2002 Jul; 25 (7): 1123-8

85. Xenical® (orlistat) capsules [prescribing information]. Revised 2003 Dec. Roche Laboratories Inc. [online]. Available from URL: http://www.fda.gov/medwatch/SAFETY/2003/03DEC_PI/Xenical_PI.pdf [Accessed 2007 Oct 15]
86. Bergholm R, Tiikkainen M, Vehkavaara S, et al. Lowering of LDL cholesterol rather than moderate weight loss improves endothelium-dependent vasodilatation in obese women with previous gestational diabetes. Diabetes Care 2003 Jun; 26 (6): 1667-72
87. Diamanti-Kandarakis E, Katsikis I, Piperi C, et al. Effect of long-term orlistat treatment on serum levels of advanced glycation end-products in women with polycystic ovary syndrome. Clin Endocrinol (Oxf) 2007 Jan; 66 (1): 103-9
88. Diamanti-Kandarakis E, Piperi C, Alexandraki K, et al. Short-term effect of orlistat on dietary glycotoxins in healthy women and women with polycystic ovary syndrome. Metabolism 2006 Apr; 55 (4): 494-500
89. Czerwienska B, Kokot F, Franek E, et al. Effect of orlistat therapy on carbohydrate, lipid, vitamin and hormone plasma levels in obese subjects [in Polish]. Pol Arch Med Wewn 2004 Dec; 112 (6): 1415-23
90. Paraskevas KI, Liapis CD, Mikhailidis DP. Leptin: a promising therapeutic target with pleiotropic action besides body weight regulation. Curr Drug Targets 2006 Jun; 7 (6): 761-71
91. Jayagopal V, Kilpatrick ES, Holding S, et al. Orlistat is as beneficial as metformin in the treatment of polycystic ovarian syndrome. J Clin Endocrinol Metab 2005 Feb; 90 (2): 729-33
92. Damci T, Yalin S, Balci H, et al. Orlistat augments postprandial increases in glucagon-like peptide 1 in obese type 2 diabetic patients. Diabetes Care 2004 May; 27 (5): 1077-80
93. Azar ST, Zantout MS. Diabetic ketoacidosis associated with orlistat treatment [letter]. Diabetes Care 2001 Mar; 24 (3): 602
94. Gonzalez-Gay MA, Garcia-Porrua C, Lueiro M, et al. Orlistat-induced cutaneous leukocytoclastic vasculitis [letter]. Arthritis Rheum 2002 Oct 15; 47 (5): 567
95. Sergeant A, Milne G, Shaffrali F. Lichenoid eruption associated with orlistat. Br J Dermatol 2006 May; 154 (5): 1020-1
96. Morotomi M, Sakaitani Y, Satou M, et al. Effects of a high-fat diet on azoxymethane-induced aberrant crypt foci and fecal biochemistry and microbial activity in rats. Nutr Cancer 1997; 27 (1): 84-91
97. Newmark HL, Yang K, Lipkin M, et al. A Western-style diet induces benign and malignant neoplasms in the colon of normal C57Bl/6 mice. Carcinogenesis 2001 Nov; 22 (11): 1871-5
98. Thornton Jr WH, MacDonald RS. Dietary fat quantity and composition induce changes in proliferation and membrane lipids in rat colon cells. Ann Nutr Metab 1997; 41 (4): 260-8
99. Garcia SB, Barros LT, Turatti A, et al. The anti-obesity agent orlistat is associated to increase in colonic preneoplastic markers in rats treated with a chemical carcinogen. Cancer Lett 2006 Aug 28; 240 (2): 221-4
100. Kridel SJ, Axelrod F, Rozenkrantz N, et al. Orlistat is a novel inhibitor of fatty acid synthase with antitumor activity. Cancer Res 2004 Mar 15; 64 (6): 2070-5
101. Menendez JA, Vellon L, Lupu R. Orlistat: from antiobesity drug to anticancer agent in Her-2/neu (erbB-2)-overexpressing gastrointestinal tumors? Exp Biol Med (Maywood) 2005 Mar; 230 (3): 151-4
102. Browne CD, Hindmarsh EJ, Smith JW. Inhibition of endothelial cell proliferation and angiogenesis by orlistat, a fatty acid synthase inhibitor. FASEB J 2006 Oct; 20 (12): 2027-35
103. Menendez JA, Vellon L, Lupu R. The antiobesity drug orlistat induces cytotoxic effects, suppresses Her-2/neu (erbB-2) oncogene overexpression, and synergistically interacts with trastuzumab (Herceptin) in chemoresistant ovarian cancer cells. Int J Gynecol Cancer 2006 Jan-Feb; 16 (1): 219-21
104. Menendez JA, Vellon L, Lupu R. Antitumoral actions of the anti-obesity drug orlistat (Xenical™) in breast cancer cells: blockade of cell cycle progression, promotion of apoptotic cell death and PEA3-mediated transcriptional repression of Her2/neu (erbB-2) oncogene. Ann Oncol 2005 Aug; 16 (8): 1253-67
105. Lupu R, Menendez JA. Pharmacological inhibitors of Fatty Acid Synthase (FASN): catalyzed endogenous fatty acid biogenesis: a new family of anti-cancer agents? Curr Pharm Biotechnol 2006 Dec; 7 (6): 483-93
106. 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 (7): 647-53
107. 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 (2): 152-9
108. McDuffie JR, Calis KA, Booth SL, et al. Effects of orlistat on fat-soluble vitamins in obese adolescents. Pharmacotherapy 2002 Jul; 22 (7): 814-22
109. Holecki M, Zahorska-Markiewicz B, Nieszporek T, et al. The influence of a 3-month weight reduction therapy with orlistat on serum vitamin B12 and folic acid concentration in obese women. Int J Obes (Lond) 2006 Jun; 30 (6): 1017-8
110. Zhi J, Melia AT, Guerciolini R, et al. The effect of orlistat on the pharmacokinetics and pharmacodynamics of warfarin in healthy volunteers. J Clin Pharmacol 1996 Jul; 36 (7): 659-66
111. MacWalter RS, Fraser HW, Armstrong KM. Orlistat enhances warfarin effect. Ann Pharmacother 2003 Apr; 37 (4): 510-2
112. Zhi J, Moore R, Kanitra L, et al. Effects of orlistat, a lipase inhibitor, on the pharmacokinetics of three highly lipophilic drugs (amiodarone, fluoxetine, and simvastatin) in healthy volunteers. J Clin Pharmacol. 2003 Apr; 43 (4): 428-35
113. Le Beller C, Bezie Y, Chabatte C, et al. Co-administration of orlistat and cyclosporine in a heart transplant recipient. Transplantation 2000 Nov 27; 70 (10): 1541-2
114. Evans S, Michael R, Wells H, et al. Drug interaction in a renal transplant patient: cyclosporine-neoral and orlistat. Am J Kidney Dis 2003 Feb; 41 (2): 493-6
115. Nagele H, Petersen B, Bonacker U, et al. Effect of orlistat on blood cyclosporine concentration in an obese heart transplant patient. Eur J Clin Pharmacol 1999 Nov; 55 (9): 667-9
116. Asberg A. Interactions between cyclosporine and lipid-lowering drugs: implications for organ transplant recipients. Drugs 2003; 63 (4): 367-78
117. Barbaro D, Orsini P, Pallini S, et al. Obesity in transplant patients: case report showing interference of orlistat with absorption of cyclosporine and review of literature. Endocr Pract 2002 Mar-Apr; 8 (2): 124-6
118. Schnetzler B, Kondo-Oestreicher M, Vala D, et al. Orlistat decreases the plasma level of cyclosporine and may be responsible for the development of acute rejection episodes. Transplantation 2000 Nov 27; 70 (10): 1540-1
119. Zhi J, Moore R, Kanitra L, et al. Pharmacokinetic evaluation of the possible interaction between selected concomitant medications and orlistat at steady state in healthy subjects. J Clin Pharmacol 2002 Sep; 42 (9): 1011-9
120. Errasti P, Garcia I, Lavilla J, et al. Reduction in blood cyclosporine concentration by orlistat in two renal transplant patients. Transplant Proc 2002 Feb; 34 (1): 137-9

121. Colman E, Fossler M. Reduction in blood cyclosporine concentrations by orlistat. N Engl J Med 2000 Apr 13; 342 (15): 1141-2

122. Bigham S, McGuigan C, MacDonald BK. Reduced absorption of lipophilic anti-epileptic medications when used concomitantly with the anti-obesity drug orlistat [letter]. Epilepsia 2006 Dec; 47 (12): 2207

123. Hilger E, Quiner S, Ginzel I, et al. The effect of orlistat on plasma levels of psychotropic drugs in patients with long-term psychopharmacotherapy. J Clin Psychopharmacol 2002 Feb; 22 (1): 68-70

124. Pavlovic ZM. Orlistat in the treatment of clozapine-induced hyperglycemia and weight gain [letter]. Eur Psychiatry 2005 Nov; 20 (7): 520

125. Peleg R. Caution when using oral contraceptive pills with Orlistat [letter]. Isr Med Assoc J 2000 Sep; 2 (9): 712

126. Hartmann D, Guzelhan C, Zuiderwijk PB, et al. Lack of interaction between orlistat and oral contraceptives. Eur J Clin Pharmacol 1996; 50 (5): 421-4

127. Madhava K, Hartley A. Hypothyroidism in thyroid carcinoma follow-up: orlistat may inhibit the absorption of thyroxine [letter]. Clin Oncol (R Coll Radiol) 2005 Sep; 17 (6): 492

128. Chaikomin R, Russo A, Rayner CK, et al. Effects of lipase inhibition on gastric emptying and alcohol absorption in healthy subjects. Br J Nutr 2006 Nov; 96 (5): 883-7

129. Melia AT, Zhi J, Zelasko R, et al. The interaction of the lipase inhibitor orlistat with ethanol in healthy volunteers. Eur J Clin Pharmacol 1998 Nov-Dec; 54 (9-10): 773-7

130. Kelley DE, Bray GA, Pi-Sunyer FX, et al. Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes: a 1-year randomized controlled trial. Diabetes Care 2002 Jun; 25 (6): 1033-41

131. Pathan MF, Latif ZA, Nazneen NE, et al. Orlistat as an adjunct therapy in type 2 obese diabetic patients treated with sulphonylurea: a Bangladesh experience. Bangladesh Med Res Counc Bull 2004 Apr; 30 (1): 1-8

132. Sari R, Balci MK, Coban E, et al. Comparison of the effect of orlistat vs orlistat plus metformin on weight loss and insulin resistance in obese women. Int J Obes Relat Metab Disord 2004 Aug; 28 (8): 1059-63

133. 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 (5): 521-5

134. Melia AT, Mulligan TE, Zhi J. The effect of orlistat on the pharmacokinetics of phenytoin in healthy volunteers. J Clin Pharmacol 1996 Jul; 36 (7): 654-8

135. Weber C, Tam YK, Schmidtke-Schrezenmeier G, et al. Effect of the lipase inhibitor orlistat on the pharmacokinetics of four different antihypertensive drugs in healthy volunteers. Eur J Clin Pharmacol 1996; 51 (1): 87-90

136. 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 (4): 352-5

137. Derosa G, Mugellini A, Ciccarelli L, et al. Randomized, double-blind, placebo-controlled comparison of the action of orlistat, fluvastatin, or both an anthropometric measurements, blood pressure, and lipid profile in obese patients with hypercholesterolemia prescribed a standardized diet. Clin Ther 2003 Apr; 25 (4): 1107-22

Correspondence: Dr *Moses S. Elisaf,* Department of Internal Medicine, Medical School, University of Ioannina, 45110 Ioannina, Greece.
E-mail: egepi@cc.uoi.gr