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Orlistat, a New Lipase Inhibitor for the Management of Obesity

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Abstract

Orlistat, a weight-loss agent with a novel mechanism of action, recently was approved by the Food and Drug Administration for the treatment of obesity. It inhibits gastric and pancreatic lipases in the lumen of the gastrointestinal tract to decrease systemic absorption of dietary fat. In several trials lasting up to 2 years, orlistat was more effective than diet alone for weight reduction and maintenance of lost weight. Orlistat treatment also results in modest improvements in total cholesterol, low-density lipoprotein, blood pressure, and fasting glucose and insulin concentrations. The major adverse effects are gastrointestinal, usually occur early in therapy and tend to decrease with continued treatment. Because orlistat may decrease the absorption of fat-soluble vitamins, a standard multiple-vitamin supplement is recommended daily during therapy to prevent abnormalities in vitamin serum concentrations. The potential for severe gastrointestinal discomfort and the modest degree of weight loss may limit the agent's clinical utility. Its long-term safety and effectiveness for weight maintenance, cost-effectiveness of treatment, and overall reduction in obesity-related morbidity and mortality remain to be determined.

Obesity is a chronic condition that affects approximately one-third of the United States population.^{1, 2} Its prevalence has increased dramatically over the past 2 decades, and it has been identified as the second most common factor contributing to preventable death in the country.^{2, 3} Obesity is a primary risk factor for the development of type 2 diabetes, hyperlipidemia, hypertension, and other cardiovascular disorders.^{4, 5} It also plays a role in the development of gallbladder disease, degenerative joint disease, respiratory disorders, and certain types of cancers.^{4, 5} As a result, the economic burden of the condition is substantial. In 1995 the total economic cost of obesity-associated disease in the United States was estimated to be \$99.2 billion.⁶

Clinical guidelines for identifying, evaluating, and treating overweight and obese adults were developed by a panel of experts convened by the National Institutes of Health.⁷ According to these guidelines, diet therapy, increased physical activity, and behavioral modification remain the mainstays of treatment. However, it was recognized that pharmacologic agents approved for long-term therapy may be useful adjuncts to diet and exercise for patients with a body mass index (BMI) of 30 kg/m² or more, and for those with a BMI above 27 kg/m² who have concomitant obesity-related risk factors or diseases.⁷ Two drugs, orlistat and sibutramine, are approved by the Food and Drug Administration (FDA) for long-term therapy of obesity.⁸ Orlistat (Xenical; Roche Pharmaceuticals, Nutley NJ), was granted approval in March 1999 for obesity management, including weight loss and weight maintenance.⁹ This agent has a novel gastrointestinal mechanism of action and is the first available antiobesity agent that does not primarily alter neurotransmitter concentrations in the central nervous system.

Chemistry

The structural formula of orlistat [(S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]-dodecyl ester] is shown in Figure 1. The drug's chemical formula is C₂₉H₅₃NO₅. It is a diastereomeric molecule with four chiral centers and a molecular weight of 495.7.

Clinical Pharmacology

Orlistat is a potent, specific, irreversible inhibitor of pancreatic and gastric lipases. Also known as tetrahydrolipstatin, it is a chemically synthesized derivative of lipstatin, which is naturally produced by *Streptomyces toxytricini*.^{10, 11} It exerts its pharmacologic activity by forming a covalent bond with the active serine site of gastric and pancreatic lipases in the lumen of the gastrointestinal tract. This action prevents these enzymes from hydrolyzing dietary fat (in the form of triglycerides) into absorbable free fatty acids and monoglycerols.¹¹⁻¹³ Undigested triglycerides are eliminated by the fecal route. Lipase inhibition induced by orlistat decreases systemic absorption of dietary fat, thereby contributing to caloric deficit. The agent does not appear to inhibit the activity of other pancreatic enzymes, such as phospholipase A₂, amylase, or trypsin.¹⁰

Data from pharmacokinetic studies using radiolabeled orlistat in both non-obese and obese individuals indicate that the drug is not appreciably absorbed into the systemic circulation.^{9, 14, 15} After single oral doses of ¹⁴C-orlistat 50 or 360 mg, maximum plasma concentrations of total radioactivity occurred within approximately 8 hours.^{14, 15} At the time of peak total radioactivity, plasma concentrations of orlistat were below the detectable assay limit of 5 ng/ml.^{9, 14, 15} In multiple-dose studies, using a more sensitive assay with a lower limit of detection equal to 0.20 ng/ml, detection of orlistat in human plasma was infrequent, with low measurable concentrations ranging from 0.20–8.8 ng/ml.^{16, 17} There was also no evidence of drug accumulation in patients treated with a dosage of 120 mg 3 times/day for up to 2 years.¹⁷ Thus all of orlistat's pharmacologic actions are believed to be exerted in the gastrointestinal tract.

Metabolism of the agent appears to occur in the gastrointestinal wall.⁹ Based on data from studies of radiolabeled orlistat in obese patients, two major metabolites were identified, M1, with a hydrolyzed 4-member lactone ring, and M3, M1 with the *N*-formal leucine moiety cleaved.¹⁵ These metabolites accounted for approximately 42% of total radioactivity in plasma, with mean concentrations of 26 ng/ml and 108 ng/ml for M1 and M3, respectively, 2–4 hours after drug administration. The primary metabolite, M1, has a relatively short half-life of approximately 3 hours; the half-life of M3 is approximately 13 hours.^{9, 15} Both M1 and M3 contain an open β -lactone ring in their chemical structures. Due to their very low plasma concentrations, and given data indicating that the β -lactone ring is required for lipase inhibition, they are considered to be pharmacologically inactive.^{9, 15, 17}

Orlistat is excreted almost completely by the fecal route.¹⁵ After an oral dose of ¹⁴C-orlistat 360 mg in normal-weight and obese subjects, approximately 97% of drug was recovered in feces, with 83% as unchanged drug.¹⁵ Less than 2% was recovered in urine, and complete excretion of total radioactivity occurred 3–5 days after administration.¹⁵

Clinical Efficacy

Short-Term Trials

Several short-term trials evaluating the efficacy of the drug for promoting weight loss in obese adults showed it to be safe and more effective than diet alone.^{18–24} These trials ranged in length from 6 weeks to 6 months, and all patients who received orlistat also were instructed to follow a hypocaloric diet with less than 30% of calories derived from fat. As expected, the most common adverse effects associated with orlistat were gastrointestinal. Results of short-term studies are shown in Table 1.^{19–21, 23, 25}

Long-Term Trials

Analysis of pooled data from five studies involving over 3000 subjects showed that orlistat-treated patients lost approximately 9% of body weight after 1 year of treatment, compared with 5.8% in placebo-treated patients. Total cholesterol and low-density lipoprotein (LDL) were significantly reduced, and diastolic blood pressure and fasting insulin and glucose concentrations decreased in orlistat-treated patients.²⁵ The agent's effects on lipoprotein concentrations appeared to be greater than expected for the degree of weight loss.

Two large, multicenter, double-blind, randomized, placebo-controlled trials administered the drug for up to 2 years. Both studies, one conducted in the United States and the other in Europe, were similar in design. The former compared orlistat with placebo for weight loss and weight maintenance in 892 obese patients (average weight 100 kg, average BMI 36 kg/m²) who were otherwise healthy.²⁶ During a 4-week, single-blind, placebo lead-in period the subjects were instructed to consume an approximately 500-kcal/day caloric-deficit diet that provided 30% of total daily calories in the form of fat. Patients with compliance of at least 70% (determined by capsule counts) were stratified according to initial weight loss (< 2 kg, 2–4 kg); 668 were randomized to receive orlistat 120 mg and 224 to receive placebo 3 times/day with meals for 1 year. The hypocaloric diet was continued throughout the first year of the study. At the end of the year, orlistat-treated patients who achieved 70%

compliance were re-randomized to receive orlistat 60 mg, orlistat 120 mg, or placebo 3 times/day for an additional year; placebo-treated patients continued to receive placebo. In an effort to stabilize body weight, the dietary intake of all subjects was modified from a hypocaloric diet to a weight-maintenance diet for the second year. All patients were required to attend dietary counseling and behavior modification sessions 4 times/year. The primary end point was change in body weight. Secondary end points included serum concentrations of total cholesterol, LDL, high-density lipoprotein (HDL), triglycerides, fasting glucose, and insulin, as well as decreases in standing waist circumference and blood pressure. Fat-soluble vitamin serum concentrations and prothrombin time (to assess vitamin K status) also were evaluated.

During the 4-week placebo lead-in, patients lost approximately 2.3 kg and had 8% decreases in total cholesterol and LDL. At the end of 1 year, 59% (133) of patients in the placebo group and 69% (458) of orlistat-treated patients remained in the study. Reasons for withdrawal were similar between groups. Orlistat-treated patients lost an average of 8.8 kg, which was statistically greater than the mean 5.8-kg loss in the placebo group ($p<0.001$). In addition, 65.5% and 38.9% of orlistat-treated patients experienced greater than 5% and greater than 10% reductions in baseline (before placebo lead-in) body weight, respectively, whereas only 43.6% and 24.8% of the placebo group achieved these degrees of weight loss.

By the end of 2 years, patients in both groups had regained some weight, but those who received orlistat 120 mg regained significantly less (35.2% regain) than those who received 60 mg (51.3%) or placebo (63.4%). Thirty-four percent of patients treated with the higher dosage of orlistat for 2 years maintained a weight loss of greater than 10% from baseline, compared with 17% of patients receiving placebo ($p=0.02$). Compared with total cholesterol measured at the end of the 4-week placebo lead-in, values increased in all groups at the end of the second year. However, patients who received orlistat 120 mg had significantly smaller increases in total cholesterol than those who received placebo (191 mg/dl increased to 195 mg/dl vs 193 mg/dl increased to 201 mg/dl, $p<0.001$). Similarly after the placebo lead-in, fasting serum glucose concentrations did not increase as much in subjects taking orlistat 120 mg as in the placebo group (101 mg/dl increased to 102 mg/dl vs 101 mg/dl increased to 104 mg/dl, $p=0.001$). Fasting insulin concentrations were reduced significantly from an average of 84 to 66.5 pmol/L with orlistat 120 mg, compared with an average of 86.4 to 86.3 pmol/L with placebo at the end of year 2. There were no differences in HDL concentrations among treatment groups, and systolic and diastolic blood pressures were essentially unchanged. Mean waist circumference decreased significantly in the orlistat-treated group (placebo 2.38 cm, orlistat 4.52 cm, $p<0.05$).²⁶

The total number of adverse events was similar between groups; however, the orlistat group reported gastrointestinal events more frequently. For example, 79% of these patients, compared with 59% of those who received placebo, reported at least one gastrointestinal adverse event. These were flatus with discharge (40.1%), oily spotting (32.7%), fecal urgency (29.7%), fatty or oily stool (19.8%), oily evacuation (14.3%), fecal incontinence (11.8%), and increased defecation (11.1%). These events were reported to be of mild to moderate intensity and decreased during the second year of treatment. Vitamin supplementation was provided for patients in whom serum vitamin concentrations fell below

the standard reference range, which included 14.1% of patients receiving orlistat 120 mg and 6.5% of those receiving placebo.²⁶

Subjects in the second study included 688 patients (average BMI 36 kg/m², average weight 99 kg) seen at obesity treatment centers throughout Europe.²⁷ After completing a 4-week placebo lead-in phase and receiving instructions to follow a hypocaloric diet, 345 patients were randomized to receive orlistat 120 mg and 343 placebo for 1 year. Patients from both groups were re-randomized at the end of the first year either to continue the same regimen or to receive the alternative treatment for an additional year. Diet was modified for weight maintenance during the second year.

Weight loss after 1 year of treatment with orlistat was slightly greater than that in the former study. These patients lost an average of 10.3 kg compared with 6.1 kg in the placebo group ($p<0.001$). Nine percent of orlistat-treated patients, compared with 2% in the placebo group, lost more than 20% of their initial body weight, and 29.5% lost between 10% and 20% compared with 15.6% in the placebo group. At the end of the trial, 57% of patients who received orlistat for 2 consecutive years maintained a weight loss of greater than 5% from baseline (before placebo lead-in). Weight regain for orlistat-treated patients who were switched to placebo during the second year was significantly greater than that for patients who continued active treatment (mean difference 2.4 kg, $p<0.001$). As was observed in the United States trial, both groups experienced significant decreases in total cholesterol and LDL during the placebo lead-in. Patients who received placebo for 2 consecutive years had gradual increases in total cholesterol and LDL toward baseline concentrations, and those who received orlistat maintained significant reductions at the end of year 2. Mean total cholesterol concentrations in the orlistat-treated group were 223 mg/dl at baseline, 208 mg/dl at the time of randomization, and 205.3 mg/dl at the end of year 2; respective mean LDL values were 147.7, 137.3, and 133.8 mg/dl. There were no significant changes in HDL levels. Blood pressure was reduced significantly in the orlistat group compared with the placebo group after 2 years, but the effect size was small. Mean diastolic and systolic blood pressures for the orlistat treatment groups were 133 and 85 mm Hg at baseline, compared with 132 and 85 mm Hg in the placebo group, 129 and 83 mm Hg at the time of randomization, compared with 128 and 85 mm Hg in the placebo group, and 127 and 80 mm Hg at the end of the trial, compared with 129 and 82 mm Hg in the placebo group.

Overall withdrawal rates were larger in the placebo group (83 patients) than in the orlistat group (61 patients). However, withdrawals due to gastrointestinal adverse events were more common with orlistat-treated patients (3.5% vs 0.6%). In general, adverse effects and vitamin replacement requirements were similar to those reported in the United States trial.

Results of these two clinical trials provide evidence that orlistat is more effective than placebo in promoting and maintaining weight loss. However, several factors should be considered when formulating clinical decisions based on these data. The drug's effects on body weight may be different in general clinical practice than in research trials. Patients enrolled in the trials were exposed to extensive and continuous dietary counseling and behavioral modification. Such resources are believed to have a substantial impact on overall weight loss but may not be readily available or consistently applied in most clinical settings.

Subjects in these trials were selected for their adherence to therapy during a 4-week lead-in period. Selection for adherence again was applied after 1 year of treatment, when subjects were rerandomized. Thus, the weight losses reported in the studies represent an ideal, and actual weight loss might be considerably smaller when orlistat is taken in the absence of organized behavioral modification and without subject selection. Total weight loss was reported from the beginning of the 4-week placebo lead-in period. The best adherence to dietary restrictions, and thus the most rapid weight loss, generally occurs in the first month of therapy. Therefore, weight reductions that can be attributed to orlistat alone may be smaller than reported in these studies. However, it should be noted that the change from a hypocaloric to a maintenance diet may have contributed to weight regain during the second year of these studies.

Orlistat may not benefit all patients. Weight loss in these studies was highly variable. In both studies weight loss was reported as means $\pm$ standard error of the mean (SEM), thereby giving the appearance of minimal variability. Conversion of data to means $\pm$ standard deviation (SD) more clearly indicates the extent of weight lost. For example, when SEM is converted to SD, the range of weight loss at the end of year 1 changed from 8.76 ± 0.37 kg to 8.76 ± 9.48 kg in the United States trial.²⁶ This suggests that some patients responded more favorably to orlistat than others. Characteristics of patients who may be more likely to respond have not been identified. Although gastrointestinal adverse effects in both studies were mild or moderate in severity, some patients may be unwilling to tolerate them, as they are more common and more severe early in treatment, before substantial weight has been lost. In the United States study, the 1-year dropout rate due to adverse effects in patients receiving orlistat was 9.1% compared with only 4.0% in the placebo group.²⁶

The results of these trials may be confounded by possible unblinding of treatment groups due to the gastrointestinal effects associated with orlistat. In the United States trial, 4.9% of patients in the placebo group dropped out during the first year due to “treatment failure,” whereas only 0.9% of orlistat-treated patients withdrew for this reason.

The drug’s long-term health benefits are unclear, as are benefits accrued from modest reductions in weight. After 2 years of continuous therapy patients lost an average of 4.5% of initial body weight (~ 4 kg).²⁶ Although modest weight reductions (5–10%) were reported to improve obesity-related risk factors,²⁸ the effect on mortality remains to be determined.

Type 2 Diabetes

The agent’s effect on weight loss and glycemic control in 322 patients with type 2 diabetes was evaluated in a 57-week, randomized, double-blind, placebo-controlled trial.²⁹ Patients (average BMI 34 kg/m^2 , body weight 99 kg) with an average hemoglobin A_{1c} (HbA_{1c}) of 8.1%, who were stabilized with either glyburide or glipizide, underwent a 5-week placebo lead-in period with a hypocaloric diet, after which 163 were randomized to receive orlistat 120 mg and 159 were randomized to receive placebo 3 times/day for 57 weeks. The primary outcome measure was body weight; secondary outcome measures were glycemic control, lipid concentrations, and waist circumference.

At the end of the 5-week placebo lead-in, both groups experienced a weight reduction of approximately 2 kg and a decrease in fasting glucose concentrations of 17–20 mg/dl. After 57 weeks of treatment, patients who received orlistat had substantially more weight loss from baseline (6.19 vs 4.31 kg, $p<0.001$), with 48.8% losing 5% or more of baseline weight, compared with 22.6% for those receiving placebo ($p<0.001$). Fasting blood glucose remained relatively constant at the end of 57 weeks (0.36 mg/dl decrease) in the orlistat group, whereas patients in the placebo group had a mean increase of 9.7 mg/dl ($p<0.001$). Orlistat-treated patients with baseline blood glucose concentrations greater than 140 mg/dl experienced the greatest benefit (mean decrease 8.4 mg/dl). They also had significantly greater reductions in HbA_{1c} concentrations (mean decrease 0.28% vs 0.18%, $p<0.001$), with patients having baseline HbA_{1c} concentrations above 8% showing the greatest benefit (mean decrease 0.53%). The average dosages of glyburide and glipizide also decreased by 23% in orlistat-treated patients compared with 9% in the placebo group ($p=0.0019$).²⁹

Adverse effects, withdrawal rates, and vitamin supplementation requirements were similar to those reported previously.^{26, 27, 29} Orlistat was effective in reducing weight and improving glycemic control in patients with type 2 diabetes. Weight loss is often more difficult for diabetic patients to achieve because several pharmacologic treatments (sulfonylureas, insulin) may result in increased weight.³⁰ Therefore, as expected, the weight loss achieved with orlistat in these patients was not as large as that in otherwise healthy obese patients.^{26, 27, 29} It may be argued that the improvement in glycemic control was merely a result of weight loss. However, the placebo group experienced an average weight loss of 4 kg at the end of the 57 weeks, and this was accompanied by increases in both fasting blood glucose and HbA_{1c} concentrations. This suggests that orlistat may have an added effect above that of diet alone in improving glycemic control. A long-term trial to assess its role in preventing the development of type 2 diabetes in obese patients is under way.

Weight Maintenance

The utility of orlistat for weight maintenance after conventional dieting was examined in a 1-year study of obese subjects who were able to lose 8% or more of their initial body weight with a 6-month hypocaloric diet.³¹ During the 6-month weight-reduction period, 1313 otherwise healthy obese subjects (BMI 28–43 kg/m²) were instructed to consume a hypocaloric diet (based on individually calculated basal metabolic rates to achieve an energy deficit of 1480 kJ/day) and received extensive dietary counseling, behavioral modification therapy, and encouragement to increase physical activity. Of the 729 subjects who reached the predetermined weight loss goal, 181 were randomized to receive orlistat 120 mg, 173 to receive orlistat 60 mg, 187 to receive orlistat 30 mg, and 188 to receive placebo 3 times/day with meals for a year. Metabolic requirements were assessed for all patients, and a maintenance diet designed to prevent further weight loss and minimize weight regain was developed for the remainder of the study. Dietary counseling and behavioral modification were continued.

The average amount of weight loss during the 6-month diet phase was 10 kg among all groups. During the ensuing year, all groups experienced weight regain. Subjects who received orlistat 120 mg regained the least amount (32.5%), which was statistically

significant compared with placebo (56% regain, $p<0.001$). Those who received orlistat 30 mg had an average regain of 53.3% from the time of randomization, and the 60-mg group regained 47.2%, consistent with a positive dose-response relationship. Total cholesterol and LDL remained 5–7% lower than baseline in all subjects treated with orlistat but increased in those receiving placebo. The group taking orlistat 120 mg recorded the greatest decreases in total cholesterol (8%) and LDL (7%) after 52 weeks. There were no significant differences among groups in HDL, blood pressure, or waist circumference. The safety and tolerability profile of orlistat was similar to that reported in previous trials.^{26, 27, 29, 31}

Results of this study suggest that orlistat 120 mg 3 times/day minimizes weight regain after conventional diet therapy. As with previous studies, these results may have been affected by the change to a maintenance diet. More favorable results may have been obtained if a hypocaloric diet were continued for longer than 6 months. The large number of patients (584) who were unable to achieve the desired weight-reduction goal with diet alone emphasizes the need for additional obesity-management options.

Drug Interactions

As many overweight or obese patients may be taking concomitant drugs for obesity-related comorbidities, it is important to consider the potential for drug interactions with orlistat. Given that orlistat is minimally absorbed, however, the potential for clinically significant systemic interactions appears to be low. Several crossover studies conducted in small numbers of normal healthy volunteers showed that orlistat does not markedly affect the pharmacokinetics of oral contraceptives, warfarin, phenytoin, digoxin, glyburide, atenolol, furosemide, nifedipine, nifedipine extended-release tablets, captopril, or ethanol.³²⁻⁴⁰ However, it did enhance the bioavailability and pharmacologic effect of pravastatin.⁹ The extent and clinical significance of this interaction remains to be determined, and the potential for drug interactions due to the pharmacologic actions of orlistat in the gastrointestinal tract requires further study. Although not well studied, the effect of dieting and dietary modification on the disposition of certain agents should be considered.

Adverse Effects

Gastrointestinal

Safety data were collected from more than 5000 patients who were treated with orlistat during clinical trials.⁹ Major adverse effects are gastrointestinal and are related to the agent's pharmacologic effect as a lipase inhibitor. The most common complaints are abdominal discomfort, liquid stools, soft stools, oily rectal spotting, flatulence and flatus with discharge, fecal urgency, fatty or oily stools, increased defecation, and fecal incontinence.^{9, 26, 27, 29, 31} At least one of these symptoms occurred in up to 95% of orlistat-treated patients during clinical trials.^{26, 27, 29, 31, 40} However, most were mild to moderate and did not persist for more than 4 weeks; they usually occurred within the first week of therapy and decreased with continued treatment.^{9, 40}

Because the drug is expected to decrease the amount of free fatty acids present in the gastrointestinal lumen by approximately 30%, theoretically it may impair gallbladder

motility and predispose patients to stone formation. In one single-dose study in adults, it did not affect gallbladder motility.⁴¹ However, the long-term effects on motility and possible sludge or gallstone formation are unknown. Safety concerns also have been raised about the potential for the development of colon cancer, osteoporosis, renal oxalate stones, and vitamin deficiency associated with long-term orlistat-induced steatorrhea.⁴²⁻⁴⁴ Postmarketing studies are necessary to evaluate the potential for these serious long-term adverse effects.

Fat-Soluble Vitamin Absorption

Orlistat inhibits pancreatic carboxylester lipase, the enzyme necessary for hydrolysis of vitamin esters and absorption of fat-soluble vitamins.^{9, 12, 13} During clinical trials, it decreased fat-soluble vitamin absorption.^{9, 26, 27, 29, 31} The effect is most notable with vitamins D and E and β -carotene.^{9, 40} Neither absorption of vitamin A nor steady-state serum concentrations of retinol appear to be significantly affected after long-term treatment.⁴⁵ In addition, although vitamin K₁ concentrations were not monitored during clinical trials, no significant alterations in prothrombin times were observed in orlistat-treated subjects.^{26, 27, 29, 31} The drug, however, does decrease the absorption of vitamin E and steady-state α -tocopherol plasma concentrations significantly.^{9, 40, 45} During clinical trials α -tocopherol concentrations decreased in orlistat-treated patients; however, plasma concentrations did not often fall below the standard reference range, and low values were corrected with vitamin E supplementation.^{26, 27, 29, 31}

Vitamin D concentrations have decreased with long-term orlistat treatment. After 2 years of therapy, subjects had an 8% decrease in 25-hydroxy-D concentrations. Calcium and parathyroid hormone concentrations were unchanged. As with vitamin E, 25-hydroxy-D concentrations remained within the normal reference range when vitamin D was supplemented.^{9, 40} Orlistat also decreases absorption of β -carotene by approximately 30%.⁴⁶ In clinical trials, this decrease was ameliorated by multivitamin supplementation.^{26, 27} Thus, a daily standard multiple-vitamin supplement is recommended during orlistat therapy to prevent abnormalities in vitamin serum concentrations.⁹

Breast Cancer Risk

In pooled data from all clinical trials evaluating orlistat, 12 cases of breast cancer were found in orlistat-treated women, compared with 2 cases in those who received placebo.^{40, 47} Most tumors were identified within 6 months of starting treatment and were sufficiently large at the time of detection that orlistat was an unlikely cause. However, because of FDA concerns that the drug, in some way, might stimulate the growth of preexisting neoplasms, an extensive retrospective analysis was conducted in an effort to interpret these findings. Evaluation of histologic tumor data from each case by an independent expert revealed significant heterogeneity among samples, as well as evidence of cancer in situ and lymph node metastases, suggesting that the development of cancerous cells predated treatment with orlistat. In more recent, prospective studies, one breast neoplasm was diagnosed in an orlistat-treated woman and six in placebo-treated women.⁴⁸ Based on this information, and in view of the drug's minimal systemic absorption, it was concluded that these findings were most likely the result of chance.^{40, 47}

Dosage and Administration

Orlistat is approved for obesity management, both weight loss and weight maintenance, in patients with an initial BMI 30 kg/m² or greater and for those with BMI 27 kg/m² or greater who have other weight-related risk factors.⁹ The lowest, maximum-effect dosage is 120 mg 3 times/day, which inhibits approximately one-third of ingested dietary fat. Therefore, the recommended dosage is 120 mg 3 times/day during or up to 1 hour after each fat-containing meal. If a meal does not contain fat or if the patient skips a meal, the dose may be omitted.⁹ The agent should be taken with a low-calorie diet containing less than 30% of calories from fat. Patients should be cautioned that taking it with a high-fat diet may result in increased gastrointestinal adverse effects. Patients also should be instructed to take a multiple vitamin at least 2 hours before or 2 hours after taking orlistat.⁹ Because systemic absorption of orlistat is negligible, no dosage adjustments are necessary for patients with impaired end-organ function. The drug is not approved for children or adolescents under age 16 years, and no studies of its benefits or risks in the pediatric population have been reported. Orlistat is available as 120-mg capsules, and the average wholesale price for 90 capsules is \$118.80.⁴⁹

Summary and Conclusion

Orlistat is the first antiobesity agent to be approved in the United States that exerts its full pharmacologic effects in the gastrointestinal tract and does not primarily alter central nervous system neurotransmitters. By inhibiting gastric and pancreatic lipases in the lumen of the gastrointestinal tract, it can prevent absorption of nearly one-third of dietary fat. When combined with diet and behavior modification, it results in significantly more weight loss than placebo and induces modest improvements in lipid profile, glucose control, and blood pressure. Orlistat may influence dietary choices because consumption of high-fat meals with the drug can lead to more severe gastrointestinal adverse effects. Whereas it appears to have a favorable safety profile, additional studies are necessary to evaluate its long-term safety and potential for interactions with other agents. Available data suggest that, in selected patients, orlistat may be an effective adjunct to diet and exercise for the management of obesity. Although its modest weight reduction may benefit obese patients, its efficacy for weight maintenance and effect on obesity-related morbidity and mortality remain to be determined. Lacking data with respect to long-term clinical outcomes, cost-effectiveness, and impact on quality of life, coupled with the necessity to take the drug 3 times/day and potentially bothersome adverse effects, may limit its clinical utility. Orlistat should be used as monotherapy for obesity, as no trials have reported its safety and efficacy in combination with anorexiants.

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Table 1.

Short-term Clinical Efficacy Studies of Orlistat

Patient Population	Study Design	Treatment Regimen	Results
17 non-obese patients with hyperlipidemia ¹⁹	16-week, 3-phase trial: 6-wk placebo run-in; 8-wk double-blind, randomized, placebo-controlled phase; 2-wk placebo follow-up	After 6-wk placebo run-in, subjects were randomized to receive orlistat 10, 30, 60, or 120 mg or placebo 3 times/day with meals for 8 wks. Patients followed low-calorie diet and were counseled by a dietitian.	Total and LDL cholesterol significantly decreased by 7.7% and 8.9%, respectively, in all orlistat-treated groups combined compared with no change with placebo. Total and LDL cholesterol returned to baseline values after 2-wk placebo follow-up.
173 non-obese patients with hyperlipidemia ²⁰	16-wk, 3-phase trial: 6-wk single blind placebo run-in; 8-wk double-blind, randomized, placebo-controlled trial; 2-wk placebo follow-up	After 6-wk placebo run-in, subjects were randomized to receive orlistat 30, 90, 180, or 360 mg/day or placebo for 8 wks. Patients consumed low-calorie diet.	Total and LDL cholesterol concentrations significantly decreased by 4–11% and 5–10%, respectively among orlistat treatment groups compared with no change in placebo group. GI adverse effects more prevalent in orlistat-treated patients; no abnormal laboratory values documented.
188 otherwise healthy obese patients ²¹	16-wk trial: 4-wk single-blind, placebo run-in; 12-wk double-blind, placebo-controlled treatment phase	After 4-wk placebo run-in, subjects were randomized to receive orlistat 10, 60, or 120 mg or placebo 3 times/day for 12 wks. Patients followed low-calorie diet and received dietary counseling.	Weight loss similar among all subjects during placebo lead-in. Subjects receiving orlistat experienced greater weight loss than those receiving placebo, with significant difference in 120-mg group compared with placebo (4.7 vs 3 kg, $p<0.001$). Total and LDL cholesterol significantly decreased with orlistat 60 and 120 mg compared with placebo. GI adverse events more common in orlistat-treated patients; no abnormal laboratory values reported.
613 otherwise healthy obese patients ²³	Dose-ranging study: 5-wk placebo lead-in; 6-mo randomized, double-blind, placebo-controlled treatment phase	After 5-wk placebo lead-in, subjects were randomized to receive orlistat 30, 60, 120, or 240 mg or placebo 3 times/day with meals for 24 wks. Patients followed low-calorie diet and received dietary counseling.	Weight loss similar (–3 kg) among all subjects during placebo lead-in. Subjects receiving orlistat (all dosages) had greater weight loss than those receiving placebo, with significant differences in 60-mg group (8.8%), 120-mg group (9.8%), and 240-mg group (9.3%) compared with placebo (6.5%). GI adverse events more common in orlistat-treated patients; no abnormal laboratory values documented.
3132 otherwise healthy obese patients ²⁵	Pooled data from 5 clinical trials, all of which included 4-wk placebo lead-in followed by 1-yr randomized, placebo-controlled, double-blind treatment phase	After 4-wk placebo lead-in, patients were randomized to receive either orlistat 120 mg or placebo 3 times/day for 1 yr. Patients followed hypocaloric diet and received dietary counseling.	Subjects receiving orlistat 120 mg had significantly more weight loss than those receiving placebo (9.2% vs 5.8%, $p<0.001$). In orlistat groups, total and LDL cholesterol significantly reduced by 1.98% and 4.23%, respectively compared with placebo (4.6% and 4.7% increase, respectively $p<0.001$) from time of randomization to end of 1 year. GI adverse events more common in orlistat-treated patients; no abnormal laboratory values documented.

GI = gastrointestinal.