

XENICAL® (orlistat)

Some patients may develop increased levels of urinary oxalate following treatment with XENICAL. Caution should be exercised when prescribing XENICAL to patients with a history of hyperoxaluria or calcium oxalate nephrolithiasis.

Weight-loss induction by XENICAL may be accompanied by improved metabolic control in diabetics, which might require a reduction in dose of oral hypoglycemic medication (e.g., sulfonylureas, metformin) or insulin (see CLINICAL STUDIES).

Misuse Potential: As with any weight-loss agent, the potential exists for misuse of XENICAL in inappropriate patient populations (eg, patients with anorexia nervosa or bulimia). See INDICATIONS AND USAGE for recommended prescribing guidelines.

Information for Patients: Patients should read the Patient Information before starting treatment with XENICAL and each time their prescription is renewed.

Drug Interactions: Alcohol: In a multiple-dose study in 30 normal weight subjects, coadministration of XENICAL and 40 grams of alcohol (e.g., approximately 3 glasses of wine) did not result in alteration of alcohol pharmacokinetics, orlistat pharmacodynamics (fecal fat excretion), or systemic exposure to orlistat.

Cyclosporine: No drug interaction studies have been conducted with XENICAL and cyclosporine. Since changes in cyclosporine absorption have been reported with variations in dietary intake, caution is advised in the concomitant use of XENICAL plus diet in patients receiving cyclosporine therapy.

Digoxin: In 12 normal-weight subjects receiving XENICAL 120 mg three times a day for 6 days, XENICAL did not alter the pharmacokinetics of a single dose of digoxin.

Fat-soluble Vitamin Supplements and Analogues: A pharmacokinetic interaction study showed a 30% reduction in beta-carotene supplement absorption when concomitantly administered with XENICAL. XENICAL inhibited absorption of a vitamin E acetate supplement by approximately 60%. The effect of orlistat on the absorption of supplemental vitamin D, vitamin A, and nutritionally-derived vitamin K is not known at this time.

Glyburide: In 12 normal-weight subjects receiving orlistat 80 mg three times a day for 5 days, orlistat did not alter the pharmacokinetics or pharmacodynamics (blood glucose-lowering) of glyburide.

Nifedipine (extended-release tablets): In 17 normal-weight subjects receiving XENICAL 120 mg three times a day for 6 days, XENICAL did not alter the bioavailability of nifedipine (extended-release tablets).

Oral Contraceptives: In 20 normal-weight female subjects, the treatment of XENICAL 120 mg three times a day for 23 days resulted in no changes in the ovulation-suppressing action of oral contraceptives.

Phenytoin: In 12 normal-weight subjects receiving XENICAL 120 mg three times a day for 7 days, XENICAL did not alter the pharmacokinetics of a single 300-mg dose of phenytoin.

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Pravastatin: In a parallel study of 24 normal-weight, mildly hypercholesterolemic subjects receiving XENICAL 120 mg three times a day for 10 days, the effect of XENICAL was additive to the lipid-lowering effect of pravastatin. Modest increases (approximately 30%) in pravastatin plasma concentrations were observed during coadministration with XENICAL.

Warfarin: In 12 normal-weight subjects, administration of XENICAL 120 mg three times a day for 16 days did not result in any change in either warfarin pharmacokinetics (both R- and S-enantiomers) or pharmacodynamics (prothrombin time and serum Factor VII). Although undercarboxylated osteocalcin, a marker of vitamin K nutritional status, was unaltered with XENICAL administration, vitamin K levels tended to decline in subjects taking XENICAL. Therefore, as vitamin K absorption may be decreased with XENICAL, patients on chronic stable doses of warfarin who are prescribed XENICAL should be monitored closely for changes in coagulation parameters.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies in rats and mice did not show a carcinogenic potential for orlistat at doses up to 1000 mg/kg/day and 1500 mg/kg/day, respectively. For mice and rats, these doses are 38 and 46 times the daily human dose calculated on a area under concentration vs time curve basis of total drug-related material.

Orlistat had no detectable mutagenic or genotoxic activity as determined by the Ames test, a mammalian forward mutation assay (V79/HPRT), an in vitro clastogenesis assay in peripheral human lymphocytes, an unscheduled DNA synthesis assay (UDS) in rat hepatocytes in culture, and an in vivo mouse micronucleus test.

When given to rats at a dose of 400 mg/kg/day in a fertility and reproduction study, orlistat had no observable adverse effects. This dose is 12 times the daily human dose calculated on a body surface area (mg/m²) basis.

Pregnancy: Teratogenic Effects: Pregnancy Category B. Teratogenicity studies were conducted in rats and rabbits at doses up to 800 mg/kg/day. Neither study showed embryotoxicity or teratogenicity. This dose is 23 and 47 times the daily human dose calculated on a body surface area (mg/m²) basis for rats and rabbits, respectively.

The incidence of dilated cerebral ventricles was increased in the mid- and high-dose groups of the rat teratology study. These doses were 6 and 23 times the daily human dose calculated on a body surface area (mg/m²) basis for the mid- and high-dose levels, respectively. This finding was not reproduced in two additional rat teratology studies at similar doses.

There are no adequate and well-controlled studies of XENICAL in pregnant women. Because animal reproductive studies are not always predictive of human response, XENICAL is not recommended for use during pregnancy.

Nursing Mothers: It is not known if orlistat is secreted in human milk. Therefore, XENICAL should not be taken by nursing women.

Pediatric Use: The safety and efficacy of XENICAL in pediatric patients have not been established.

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Geriatric Use: Clinical studies of XENICAL did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

ADVERSE REACTIONS: Commonly Observed (based on first year and second year data - XENICAL 120 mg three times a day versus placebo):

Gastrointestinal (GI) symptoms were the most commonly observed treatment-emergent adverse events associated with the use of XENICAL in double-blind, placebo-controlled clinical trials and are primarily a manifestation of the mechanism of action. (Commonly observed is defined as an incidence of $\geq 5\%$ and an incidence in the XENICAL 120 mg group that is at least twice that of placebo.)

Table 7. Commonly Observed Adverse Events

Adverse Event	Year 1		Year 2	
	XENICAL* % Patients (N=1913)	Placebo* % Patients (N=1466)	XENICAL* % Patients (N=613)	Placebo* % Patients (N=524)
Oily Spotting	26.6	1.3	4.4	0.2
Flatus with Discharge	23.9	1.4	2.1	0.2
Fecal Urgency	22.1	6.7	2.8	1.7
Fatty/Oily Stool	20.0	2.9	5.5	0.6
Oily Evacuation	11.9	0.8	2.3	0.2
Increased Defecation	10.8	4.1	2.6	0.8
Fecal Incontinence	7.7	0.9	1.8	0.2

*Treatment designates XENICAL three times a day plus diet or placebo plus diet

These and other commonly observed adverse reactions were generally mild and transient, and they decreased during the second year of treatment. In general, the first occurrence of these events was within 3 months of starting therapy. Overall, approximately 50% of all episodes of GI adverse events associated with orlistat treatment lasted for less than 1 week, and a majority lasted for no more than 4 weeks. However, GI adverse events may occur in some individuals over a period of 6 months or longer.

Discontinuation of Treatment: In controlled clinical trials, 8.8% of patients treated with XENICAL discontinued treatment due to adverse events, compared with 5.0% of placebo-treated patients. For XENICAL, the most common adverse events resulting in discontinuation of treatment were gastrointestinal.

Incidence in Controlled Clinical Trials: The following table lists other treatment-emergent adverse events from seven multicenter, double-blind, placebo-controlled clinical trials that occurred at a frequency of $\geq 2\%$ among patients treated with XENICAL 120 mg three times a day and with an incidence that was greater than placebo during year 1 and year 2, regardless of relationship to study medication.

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Table 8. Other Treatment-Emergent Adverse Events From Seven Placebo-Controlled Clinical Trials

Body System/Adverse Event	Year 1		Year 2	
	XENICAL* % Patients (N=1913)	Placebo* % Patients (N=1466)	XENICAL* % Patients (N=613)	Placebo* % Patients (N=524)
<i>Gastrointestinal System</i>				
Abdominal Pain/Discomfort	25.5	21.4	-	-
Nausea	8.1	7.3	3.6	2.7
Infectious Diarrhea	5.3	4.4	-	-
Rectal Pain/Discomfort	5.2	4.0	3.3	1.9
Tooth Disorder	4.3	3.1	2.9	2.3
Gingival Disorder	4.1	2.9	2.0	1.5
Vomiting	3.8	3.5	-	-
<i>Respiratory System</i>				
Influenza	39.7	36.2	-	-
Upper Respiratory Infection	38.1	32.8	26.1	25.8
Lower Respiratory Infection	7.8	6.6	-	-
Ear, Nose & Throat Symptoms	2.0	1.6	-	-
<i>Musculoskeletal System</i>				
Back Pain	13.9	12.1	-	-
Pain Lower Extremities	-	-	10.8	10.3
Arthritis	5.4	4.8	-	-
Myalgia	4.2	3.3	-	-
Joint Disorder	2.3	2.2	-	-
Tendonitis	-	-	2.0	1.9
<i>Central Nervous System</i>				
Headache	30.6	27.6	-	-
Dizziness	5.2	5.0	-	-
<i>Body as a Whole</i>				
Fatigue	7.2	6.4	3.1	1.7
Sleep Disorder	3.9	3.3	-	-
<i>Skin & Appendages</i>				
Rash	4.3	4.0	-	-
Dry Skin	2.1	1.4	-	-
<i>Reproductive, Female</i>				
Menstrual Irregularity	9.8	7.5	-	-
Vaginitis	3.8	3.6	2.6	1.9
<i>Urinary System</i>				
Urinary Tract Infection	7.5	7.3	5.9	4.8
<i>Psychiatric Disorder</i>				
Psychiatric Anxiety	4.7	2.9	2.8	2.1
Depression	-	-	3.4	2.5

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Body System/Adverse Event	Year 1		Year 2	
	XENICAL* % Patients (N=1913)	Placebo* % Patients (N=1466)	XENICAL* % Patients (N=613)	Placebo* % Patients (N=524)
<i>Hearing & Vestibular Disorders</i>				
Otitis	4.3	3.4	2.9	2.5
<i>Cardiovascular Disorders</i>				
Pedal Edema	-	-	2.8	1.9

* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet

- None reported at a frequency $\geq 2\%$ and greater than placebo

OVERDOSAGE: Single doses of 800 mg XENICAL and multiple doses of up to 400 mg three times a day for 15 days have been studied in normal weight and obese subjects without significant adverse findings.

Should a significant overdose of XENICAL occur, it is recommended that the patient be observed for 24 hours. Based on human and animal studies, systemic effects attributable to the lipase-inhibiting properties of orlistat should be rapidly reversible.

DOSAGE AND ADMINISTRATION: The recommended dose of XENICAL is one 120 mg capsule three times a day with each main meal containing fat (during or up to 1 hour after the meal).

The patient should be on a nutritionally balanced, reduced-calorie diet that contains approximately 30% of calories from fat. The daily intake of fat, carbohydrate, and protein should be distributed over three main meals. If a meal is occasionally missed or contains no fat, the dose of XENICAL can be omitted.

Because XENICAL has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene, patients should be counseled to take a multivitamin containing fat-soluble vitamins to ensure adequate nutrition. The supplement should be taken at least 2 hours before or after the administration of XENICAL, such as at bedtime.

Doses above 120 mg three times a day have not been shown to provide additional benefit.

Based on fecal fat measurements, the effect of XENICAL is seen as soon as 24 to 48 hours after dosing. Upon discontinuation of therapy, fecal fat content usually returns to pretreatment levels within 48 to 72 hours.

The safety and effectiveness of XENICAL beyond 2 years have not been determined at this time.

HOW SUPPLIED: XENICAL is a dark-blue, hard-gelatin capsule containing pellets of powder.

XENICAL 120 mg Capsules: Dark-blue, two-piece, No. 1 opaque hard-gelatin capsule imprinted with Roche and XENICAL 120 in light-blue ink — bottle of 90 (NDC 0004-0256-52).

Storage Conditions: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. **Keep bottle tightly closed.**

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XENICAL should not be used after the given expiration date.



Pharmaceuticals

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TO PHARMACIST: PLEASE PROVIDE THIS INFORMATION TO THE PATIENT. ALSO REFER PATIENT TO ADDITIONAL PATIENT INFORMATION CONCERNING GI EFFECTS UNDER THE PEEL-AWAY LABEL.



Important Patient Information

Patient Information about XENICAL[®] (orlistat) Capsules

XENICAL (zen' i-cal)
Generic Name: orlistat

Please read this information before you start taking XENICAL and each time you renew your prescription. This important information may help you successfully lose weight and maintain your weight loss while taking XENICAL. This patient information is a summary and is not intended to take the place of discussions with your doctor. It does not list all benefits and risks of XENICAL. The medication described here can only be prescribed and dispensed by a licensed health care professional, who has information about your medical condition and more information about the drug, including how to take it, what to expect, and potential side effects. If you have any questions about XENICAL, talk with your doctor.

What is XENICAL?

XENICAL is an oral prescription weight loss medication used to help obese people lose weight and keep this weight off. XENICAL works in your intestines, where it blocks some of the fat you eat from being absorbed. This undigested fat is then eliminated in your bowel movements. XENICAL should be used together with a reduced-calorie diet that your doctor will recommend.

Excess weight has been proven to contribute to an increased risk of developing many medical problems, including high blood pressure, high cholesterol, heart disease, and diabetes. The consumption of excess fatty food and calories plays a significant role in the development of excess weight. While fat is an important component of a balanced diet, the consumption of excess fat contributes to excess body weight, since fat provides twice the number of calories per gram of weight as carbohydrates and protein. Reduction of dietary fat intake is one potential way of losing weight.

How does XENICAL work?

If you eat an excess amount of fat or calories, the excess is stored as fat by the body resulting in weight gain. When you eat fat, your body breaks it down into its simplest components so that it can be absorbed. Enzymes in your intestinal tract, called lipases, help digest (or breakdown) fat. When you take XENICAL with meals, XENICAL attaches to the lipases and blocks them from breaking down some of the fat you have eaten. The undigested fat cannot be absorbed and is eliminated in your bowel movements. By working this way, XENICAL helps block about 30% of the fat eaten in food from being absorbed by your body.

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Following one year of treatment, XENICAL in combination with diet was shown to be more effective in reducing weight than diet alone. In most cases, weight loss was gradual. Patients treated with XENICAL and a reduced-calorie diet for one year lost an average of 13.4 pounds while those on a reduced-calorie diet alone lost 5.8 pounds.

Who should use XENICAL?

A weight loss program that includes a reduced-calorie diet and appropriate physical activity may be adequate in some patients. You should discuss with your doctor or other health care provider whether XENICAL should be added to such a program.

XENICAL may be right for you if you are considerably overweight (at least 30% above ideal weight or a body mass index of 30 or greater). XENICAL may also be right for you if you are overweight (at least 20% above ideal weight or a body mass index of 27 or greater) and also have other risk factors such as high blood pressure, high cholesterol, heart disease, or diabetes.

How to determine your body mass index (BMI):

The chart below illustrates BMI according to a variety of weights and heights. The BMI is calculated by dividing your weight in kilograms by your height in meters squared. To use this chart:

- Find the height closest to your height in the left-hand column.
- Then move across the top row to find the weight closest to your weight.
- The number where these two meet is your BMI. (For example, a person who weighs 180 lbs and is 5'5" would have a BMI of 30.)

		WEIGHT (lb)																				
		120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280	290	300	310	320
HEIGHT (ft/in)	4'10"	25	27	29	31	34	36	38	40	42	44	46	48	50	52	54	57	59	61	63	65	67
	4'11"	24	26	28	30	32	34	36	38	40	43	45	47	49	51	53	55	57	59	61	63	65
	5'0"	23	25	27	29	31	33	35	37	39	41	43	45	47	49	51	53	55	57	59	61	63
	5'1"	23	25	27	28	30	32	34	36	38	40	42	44	45	47	49	51	53	55	57	59	61
	5'2"	22	24	26	27	29	31	33	35	37	38	40	42	44	46	48	49	51	53	55	57	59
	5'3"	21	23	25	27	28	30	32	34	36	37	39	41	43	44	46	48	50	51	53	55	57
	5'4"	21	22	24	26	28	29	31	33	34	36	38	40	41	43	45	46	48	50	52	53	55
	5'5"	20	22	23	25	27	28	30	32	33	35	37	38	40	42	43	45	46	48	50	52	53
	5'6"	19	21	23	24	26	27	29	31	32	34	36	37	39	40	42	44	45	47	49	50	52
	5'7"	19	20	22	24	25	27	28	30	31	33	35	36	38	39	41	42	44	46	47	49	50
	5'8"	18	20	21	23	24	26	27	29	30	32	34	35	37	38	40	41	43	44	46	47	49
	5'9"	18	19	21	22	24	25	27	28	30	31	33	34	36	37	38	40	41	43	44	46	47
	5'10"	17	19	20	22	23	24	26	27	29	30	32	33	35	36	37	39	40	42	43	45	46
	5'11"	17	18	20	21	22	24	25	27	28	29	31	32	34	35	36	38	39	41	42	43	45
	6'0"	16	18	19	20	22	23	24	26	27	29	30	31	33	34	35	37	38	39	41	42	43
	6'1"	16	17	19	20	21	22	24	25	26	28	29	30	32	33	34	36	37	38	40	41	42
	6'2"	15	17	18	19	21	22	23	24	26	27	28	30	31	32	33	35	36	37	39	40	41

Who should not use XENICAL?

Those who:

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- consistently have problems absorbing food (chronic malabsorption); or
- have gallbladder problems; or
- are pregnant or are breastfeeding a child; or
- have ever had an allergic reaction to orlistat or any of the inactive ingredients in XENICAL.

What should I tell my doctor before taking XENICAL?

Before beginning treatment with XENICAL, make sure your doctor knows if you are:

- allergic to any medicines, foods, or dyes;
- taking any other weight-loss medication;
- taking cyclosporine;
- taking any other medicines (including those not prescribed by your doctor);
- taking any dietary supplements, including herbal products;
- planning to become pregnant; or
- anorexic or bulimic.

This information will help you and your physician decide if the expected advantages of XENICAL are greater than any possible disadvantages.

How should I take XENICAL?

The recommended dose is one 120 mg capsule by mouth with liquid at each main meal that contains fat. You can take XENICAL in conjunction with a mildly reduced-calorie diet up to 3 times a day. Each time you take XENICAL, your meal should contain no more than about 30% of calories from fat. Take XENICAL during meals or up to one hour after a meal. If you occasionally miss a meal or have a meal without fat, you can omit your dose of XENICAL. Doses greater than 120 mg three times a day have not been shown to provide an additional weight loss benefit.

You should use XENICAL together with a nutritionally balanced, mildly reduced-calorie diet that contains no more than about 30% of calories from fat. You should evenly divide your daily intake of fat, carbohydrates, and protein over 3 main meals.

You should try to follow a healthy eating plan such as the one developed by the American Heart Association. Following this eating plan will help you lose weight while decreasing some of the possible gastrointestinal effects you may experience while taking XENICAL.

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IF YOUR DAILY CALORIE LEVEL IS:	THE RECOMMENDED DAILY GRAMS OF FAT (in a 30% fat diet) ARE:
1500	50
1600	53
1800	60
2000	67

Should I take a multivitamin with XENICAL?

XENICAL interferes with your body's absorption of some fat-soluble vitamins. Therefore, when you use XENICAL, you should take a daily multivitamin supplement that contains vitamins D, E, K, and beta-carotene. Take your multivitamin once a day at least 2 hours before or after taking XENICAL, such as at bedtime.

Can I take XENICAL while taking other medications?

Be sure to discuss with your doctor all medications (including herbal products) you are currently taking, including medicines you can get without a prescription (over-the-counter), to determine if XENICAL can be taken in addition to these medications.

How long should I use XENICAL?

The use of XENICAL for more than 2 years has not been studied. You and your doctor should discuss how long you should use XENICAL.

What are the most common side effects of XENICAL?

Because XENICAL works by blocking the absorption of dietary fat, it is likely that you will experience some changes in bowel habits. These generally occur during the first weeks of treatment; however, they may continue throughout your use of XENICAL. These changes may include oily spotting, gas with discharge, urgent need to go to the bathroom, oily or fatty stools, an oily discharge, increased number of bowel movements, and inability to control bowel movements. Due to the presence of undigested fat, the oil seen in a bowel movement may be clear or have a coloration such as orange or brown.

These bowel changes are a natural effect of blocking the fat from being absorbed and indicate that XENICAL is working. They generally occur early in treatment, particularly after meals containing higher amounts of fat than are recommended. These symptoms are often temporary and may lessen or disappear as you continue treatment and keep to your recommended diet of meals containing no more than about 30% fat. However, these side effects may occur in some individuals over a period of 6 months or longer.

If you are concerned about these or any other side effects you experience while taking XENICAL, talk to your doctor or pharmacist.

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What lifestyle changes should I consider when taking XENICAL?

You must use XENICAL with a recommended mildly reduced-calorie diet. You should also follow a program of regular physical activity, such as walking. **However, before you undertake any activity or exercise program, be sure to speak with your doctor or health care professional.**

How can I reduce dietary fat?

To help you get started on reducing the fat in your diet to around 30%, read the labels on all the foods you buy. You should avoid foods that contain more than 30% fat while you are taking XENICAL.

- When eating meat, poultry or fish, limit your portion to 2 or 3 ounces (roughly the size of a deck of cards). Choose lean cuts of meat and remove the skin from poultry. Fill up your meal plate by including more grains, fruits, and vegetables.
- Replace whole-milk products with nonfat or 1% milk and nonfat, reduced-fat, or low-fat dairy items.
- Cook with less fat. Use vegetable oil spray when cooking. Salad dressings, many baked items, and prepackaged, processed, and fast foods are usually high in fat. Use the low- or non-fat versions and/or cut back on serving sizes.
- When dining out, ask how foods are prepared and request that they be prepared with little or no added fat.

Call 1-800-437-8251 today to join the XeniCareSM program, and receive valuable information tailored to your lifestyle that may help you successfully lose weight and maintain your weight loss while taking XENICAL.



Pharmaceuticals

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