

**IMPORTANT
DRUG
WARNING**

May 2012

Subject: Important Changes in the XENICAL (orlistat) Prescribing Information—Contraindication in Pregnancy, Updated Safety Information, and New Label Format

Dear Healthcare Professional,

XENICAL® (orlistat) is a reversible inhibitor of gastrointestinal lipases and is indicated for obesity management. Genentech would like to inform you of important safety information concerning XENICAL that has been added or revised in the prescribing information which is now in the Physician Labeling Rule (PLR) label format. XENICAL is now contraindicated for use during pregnancy. There is also new safety information regarding lower gastrointestinal bleeding, and clarifying information regarding renal function and interactions with cyclosporine.

These important safety changes to the XENICAL prescribing information are described below in Sections 4, 5, 6, and 8 of the XENICAL label.

CONTRAINDICATIONS (Section 4) and USE IN SPECIFIC POPULATIONS (Section 8)
Contraindication for Use in Pregnancy:

Sections 4 and 8.1 of the revised labeling include the use in pregnancy as a contraindication and a revision of the Pregnancy Category from “B” to “X.”

XENICAL is contraindicated during pregnancy because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm. A minimum weight gain, and no weight loss, is currently recommended for all pregnant women. This includes those who are already overweight or obese.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be told about the potential hazard of maternal weight loss to the fetus.

WARNINGS AND PRECAUTIONS (Section 5):
Revised Information on Renal and Urinary Oxalate:

Section 5.3 of the revised labeling includes updated information on potential renal effects of XENICAL. Cases of oxalate nephrolithiasis and acute oxalate nephropathy with renal failure after treatment with XENICAL have been reported in patients with, or at risk for, renal disease.

XENICAL should be used with caution in those with a history of hyperoxaluria or calcium oxalate nephrolithiasis. It is recommended that renal function be monitored when prescribing XENICAL to patients at risk for renal impairment.

Revised Recommendations on using XENICAL with Cyclosporine:

Section 5.1 of the revised prescribing information includes new details from a clinical trial evaluating the impact of XENICAL on cyclosporine plasma levels. To reduce the chance of a drug-drug interaction, cyclosporine should be taken at least 3 hours before or after XENICAL in patients receiving both XENICAL and cyclosporine therapy. In addition, in patients whose cyclosporine levels are being measured, more frequent monitoring should be considered.

ADVERSE REACTIONS (Section 6)

Addition of a New Adverse Reaction of Lower GI Bleeding:

In section 6.2, **Postmarketing Surveillance**, information has been added on cases of lower gastrointestinal bleeding reported in patients treated with XENICAL. Most reports are non-serious. Any severe or persistent cases should be investigated further.

Background

As per Federal Regulations regarding labels for prescription products, product labels are being updated to conform to the new PLR label format. The XENICAL professional label has now been converted to the new format. During this collaborative process with FDA, it was agreed that the current XENICAL label should include additional information related to pregnancy, information regarding lower GI bleeding, and clarification of information regarding cyclosporine drug interactions and renal function and symptoms of kidney problems.

For additional information on XENICAL's indication and important safety information, as well as the full prescribing information, please see the XENICAL Prescribing Information enclosed with this letter or visit www.gene.com.

If you have any questions or require additional information regarding the use of XENICAL, please contact our Medical Communications Group at 1-800-821-8590 from 5:30 AM to 4:00 PM Pacific Time, Monday through Friday.

As always, healthcare professionals are encouraged to report side effects associated with the use of XENICAL to Genentech at 1-888-835-2555. Alternatively, such information may be reported to FDA's MedWatch Safety Information and Adverse Event Reporting Program, either online at www.fda.gov/medwatch, by telephone (1-800-FDA-1088), by facsimile (1-800-FDA-0178), or by mail using the MedWatch Form FDA 3500 (FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville MD 20852-9787).

Sincerely,



Hal Barron, MD
Executive Vice President
Head, Global Development
Chief Medical Officer

Summary of Important Information about XENICAL (orlistat)

XENICAL is contraindicated in patients:

- who are pregnant. Weight loss offers no potential benefit to a pregnant woman and may result in fetal harm. A minimum weight gain, and no weight loss, is currently recommended for all pregnant women, including those who are already overweight or obese, due to the obligatory weight gain that occurs in maternal tissues during pregnancy.
- with chronic malabsorption syndrome
- with cholestasis
- with known hypersensitivity to XENICAL or to any component of this product

Warnings and Precautions:

- XENICAL can decrease cyclosporine exposure. XENICAL and cyclosporine should not be simultaneously co-administered.
- Patients should be strongly encouraged to take a multivitamin supplement that contains fat-soluble vitamins to ensure adequate nutrition because XENICAL has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene.
- Rare cases of severe liver injury with hepatocellular necrosis or acute hepatic failure have been reported, with some of these cases resulting in liver transplant or death.
- Patients may develop increased levels of urinary oxalate following treatment with XENICAL. Monitor renal function in patients at risk for renal insufficiency.
- Substantial weight loss can increase the risk of cholelithiasis.
- Exclude organic causes of obesity (eg, hypothyroidism) before prescribing XENICAL.
- Patients should be advised to adhere to dietary guidelines. Gastrointestinal events may increase when XENICAL is taken with a diet high in fat (>30% total daily calories from fat).

It is not known if XENICAL is present in human milk. Caution should be exercised when XENICAL is administered to a nursing woman.

The most commonly observed adverse events (incidence of $\geq 5\%$ and twice that of placebo) were oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, increased defecation and fecal incontinence. 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 XENICAL 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.