CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-766/S-021

Trade Name: Xenical Capsules

Generic Name: Orlistat

Sponsor: Hoffman LaRoche, Inc.

Approval Date: September 2, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-766/S-021

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-766/ S-021

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-766/S-021

Hoffman-LaRoche, Inc.
Attention: Margaret J. Jack
Program Director
340 Kingsland Street
Nutley, New Jersey, 07110-1199

Dear Ms. Jack:

Please refer to your supplemental new drug application dated March 3, 2005, received March 4, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xenical (orlistat) Capsules, 120 mg.

This "Changes Being Effected" supplemental new drug application provides for labeling changes to the ADVERSE REACTIONS section of the label in the subsection entitled Other Clinical Studies or Postmarketing Surveillance.

We completed our review of this application and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. For administrative purposes, designate this submission "**FPL for approved supplement NDA 20-766/S-021**." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Oluchi Elekwachi, PharmD, MPH , Regulatory Project Manager, at (301) 827-6381.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Labeling Package Insert (PI)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Orloff
9/2/2005 04:15:59 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-766/S-021

APPROVED LABELING

Xenical® (orlistat)
Capsules 120 mg

XENICAL®

(orlistat)

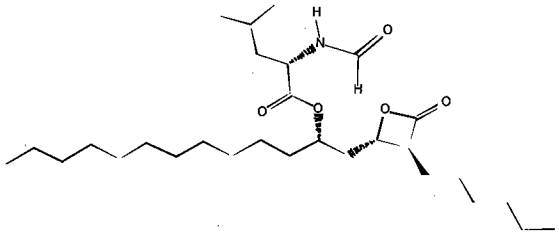
CAPSULES

R_x only

DESCRIPTION

XENICAL (orlistat) is a lipase inhibitor for obesity management that acts by inhibiting the absorption of dietary fats.

Orlistat is (S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl] methyl]-dodecyl ester. Its empirical formula is $C_{29}H_{53}NO_5$, and its molecular weight is 495.7. It is a single diastereomeric molecule that contains four chiral centers, with a negative optical rotation in ethanol at 529 nm. The structure is:



Orlistat is a white to off-white crystalline powder. Orlistat is practically insoluble in water, freely soluble in chloroform, and very soluble in methanol and ethanol. Orlistat has no pK_a within the physiological pH range.

XENICAL is available for oral administration in dark-blue, hard-gelatin capsules, with light-blue imprinting. Each capsule contains 120 mg of the active ingredient, orlistat. The capsules also contain the inactive ingredients microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, povidone, and talc. Each capsule shell contains gelatin, titanium dioxide, and FD&C Blue No.1, with printing of pharmaceutical glaze NF, titanium dioxide, and FD&C Blue No.1 aluminum lake.

CLINICAL PHARMACOLOGY

Mechanism of Action

Orlistat is a reversible inhibitor of lipases. It exerts its therapeutic activity in the lumen of the stomach and small intestine by forming a covalent bond with the active serine residue site of gastric and pancreatic lipases. The inactivated enzymes are thus unavailable to hydrolyze dietary fat in the form of triglycerides into absorbable free fatty acids and monoglycerides. As undigested triglycerides are not absorbed, the resulting caloric deficit may have a positive effect on weight control. Systemic absorption of the drug is therefore not needed for activity. At the recommended therapeutic dose of 120 mg three times a day, orlistat inhibits dietary fat absorption by approximately 30%.

Absorption

Systemic exposure to orlistat is minimal. Following oral dosing with 360 mg ^{14}C-orlistat, plasma radioactivity peaked at approximately 8 hours; plasma concentrations of intact orlistat were near the limits of detection (<5 ng/mL). In therapeutic studies involving monitoring of plasma samples, detection of intact orlistat in plasma was sporadic and concentrations were low (<10 ng/mL or 0.02 μM), without evidence of accumulation, and consistent with minimal absorption.

The average absolute bioavailability of intact orlistat was assessed in studies with male rats at oral doses of 150 and 1000 mg/kg/day and in male dogs at oral doses of 100 and 1000 mg/kg/day and found to be 0.12%, 0.59% in rats and 0.7%, 1.9% in dogs, respectively.

Distribution

In vitro orlistat was >99% bound to plasma proteins (lipoproteins and albumin were major binding proteins). Orlistat minimally partitioned into erythrocytes.

Metabolism

Based on animal data, it is likely that the metabolism of orlistat occurs mainly within the gastrointestinal wall. Based on an oral ^{14}C-orlistat mass balance study in obese patients, two metabolites, M1 (4-member lactone ring hydrolyzed) and M3 (M1 with N-formyl leucine moiety cleaved), accounted for approximately 42% of total radioactivity in plasma. M1 and M3 have an open β-lactone ring and extremely weak lipase inhibitory activity (1000- and 2500-fold less than orlistat, respectively). In view of this low inhibitory activity and the low plasma levels at the therapeutic dose (average of 26 ng/mL and 108 ng/mL for M1 and M3, respectively, 2 to 4 hours after a dose), these metabolites are considered pharmacologically inconsequential. The primary metabolite M1 had a short half-life (approximately 3 hours) whereas the secondary metabolite M3 disappeared at a slower rate (half-life approximately 13.5 hours). In obese patients, steady-state plasma levels of M1, but not M3, increased in proportion to orlistat doses.

Elimination

Following a single oral dose of 360 mg ^{14}C-orlistat in both normal weight and obese subjects, fecal excretion of the unabsorbed drug was found to be the major route of elimination. Orlistat and its M1 and M3 metabolites were also subject to biliary excretion. Approximately 97% of the administered radioactivity was excreted in feces; 83% of that was found to be unchanged orlistat. The cumulative renal excretion of total radioactivity was <2% of the given dose of 360 mg ^{14}C-orlistat. The time to reach complete excretion (fecal plus urinary) was 3 to 5 days. The disposition of orlistat appeared to be similar between normal weight and obese subjects. Based on limited data, the half-life of the absorbed orlistat is in the range of 1 to 2 hours.

Special Populations

Because the drug is minimally absorbed, studies in special populations (geriatric, different races, patients with renal and hepatic insufficiency) were not conducted.

Pediatrics

Plasma concentrations of orlistat and its metabolites M1 and M3 were similar to those found in adults at the same dose level. Daily fecal fat excretions were 27% and 7% of dietary intake in orlistat and placebo treatment groups, respectively.

Drug-Drug Interactions

Drug-drug interaction studies indicate that XENICAL had no effect on pharmacokinetics and/or pharmacodynamics of alcohol, digoxin, glyburide, nifedipine (extended-release tablets), oral contraceptives, phenytoin, pravastatin, or warfarin. Alcohol did not affect the pharmacodynamics of orlistat.

Other Short-term Studies

Adults

In several studies of up to 6-weeks duration, the effects of therapeutic doses of XENICAL on gastrointestinal and systemic physiological processes were assessed in normal-weight and obese subjects. Postprandial cholecystokinin plasma concentrations were lowered after multiple doses of XENICAL in two studies but not significantly different from placebo in two other experiments. There were no clinically significant changes observed in gallbladder motility, bile composition or lithogenicity, or colonic cell proliferation rate, and no clinically significant reduction of gastric emptying time or gastric acidity. In addition, no effects on plasma triglyceride levels or systemic lipases were observed with the administration of XENICAL in these studies. In a 3-week study of 28 healthy male volunteers, XENICAL (120 mg three times a day) did not significantly affect the balance of calcium, magnesium, phosphorus, zinc, copper, and iron.

Pediatrics

In a 3-week study of 32 obese adolescents aged 12 to 16 years, XENICAL (120 mg three times a day) did not significantly affect the balance of calcium, magnesium, phosphorus, zinc, or copper. The iron balance was decreased by 64.7 μmole/24 hours and 40.4 μmole/24 hours in orlistat and placebo treatment groups, respectively.

Dose-response Relationship

A simple maximum effect (E_{max}) model was used to define the dose-response curve of the relationship between XENICAL daily dose and fecal fat excretion as representative of gastrointestinal lipase inhibition. The dose-response curve demonstrated a steep portion for doses up to approximately 400 mg daily, followed by a plateau for higher doses. At doses greater than 120 mg three times a day, the percentage increase in effect was minimal.

Observational epidemiologic studies have established a relationship between obesity and visceral fat and the risks for cardiovascular disease, type 2 diabetes, certain forms of cancer, gallstones, certain respiratory disorders, and an increase in overall mortality. These studies suggest that weight loss, if maintained, may produce health benefits for obese patients who have or are at risk of developing weight-related comorbidities. The long-term effects of orlistat on morbidity and mortality associated with obesity have not been established.

The effects of XENICAL on weight loss, weight maintenance, and weight regain and on a number of comorbidities (eg, type 2 diabetes, lipids, blood pressure) were assessed in the 4-year XENDOS study and in seven long-term (1- to 2-years duration) multicenter, double-blind, placebo-controlled clinical trials. During the first year of therapy, the studies of 2-year duration assessed weight loss and weight maintenance. During the second year of therapy, some studies assessed continued weight loss and weight maintenance and others assessed the effect of orlistat on weight regain. These studies included over 2800 patients treated with XENICAL and 1400 patients treated with placebo. The majority of these patients had obesity-related risk factors and comorbidities. In the XENDOS study, which included 3304 patients, the time to onset of type 2 diabetes was assessed in addition to weight management. In all these studies, treatment with XENICAL and placebo designates treatment with XENICAL plus diet and placebo plus diet, respectively.

During the weight loss and weight maintenance period, a well-balanced, reduced-calorie diet that was intended to result in an approximate 20% decrease in caloric intake and provide 30% of calories from fat was recommended to all patients. In addition, all patients were offered nutritional counseling.

One-year Results: Weight Loss, Weight Maintenance, and Risk Factors

Weight loss was observed within 2 weeks of initiation of therapy and continued for 6 to 12 months.

Pooled data from five clinical trials indicated that the overall mean weight loss from randomization to the end of 6 months and 1 year of treatment in the intent-to-treat population were 12.4 lbs and 13.4 lbs in the patients treated with XENICAL and 6.2 lbs and 5.8 lbs in the placebo-treated patients, respectively. During the 4-week placebo lead-in period of the studies, an additional 5 to 6 lb weight loss was also observed in the same patients. Of the patients who completed 1 year of treatment, 57% of the patients treated with XENICAL (120 mg three times a day) and 31% of the placebo-treated patients lost at least 5% of their baseline body weight.

The percentages of patients achieving ≥5% and ≥10% weight loss after 1 year in five large multicenter studies for the intent-to-treat populations are presented in Table 1.

Table 1 **Percentage of Patients Losing ≥5% and ≥10% of Body Weight From Randomization After 1-Year Treatment***

Intent-to-Treat Population†										
	≥5% Weight Loss					≥10% Weight Loss				
Study No.	XENICAL	n	Placebo	n	p-value	XENICAL	n	Placebo	n	p-value
14119B	35.5%	110	21.3%	108	0.021	16.4%	110	6.5%	108	0.022
14119C	54.8%	343	27.4%	340	<0.001	24.8%	343	8.2%	340	<0.001
14149	50.6%	241	26.3%	236	<0.001	22.8%	241	11.9%	236	0.02
14161‡	37.1%	210	16.0%	212	<0.001	19.5%	210	3.8%	212	<0.001
14185	42.6%	657	22.4%	223	<0.001	17.7%	657	9.9%	223	0.006

The diet utilized during year 1 was a reduced-calorie diet.

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

† Last observation carried forward

‡ All studies, with the exception of 14161, were conducted at centers specialized in treating obesity and complications of obesity. Study 14161 was conducted with primary care physicians.

The relative changes in risk factors associated with obesity following 1 year of therapy with XENICAL and placebo are presented for the population as a whole and for the population with abnormal values at randomization.

Population as a Whole

The changes in metabolic, cardiovascular and anthropometric risk factors associated with obesity based on pooled data for five clinical studies, regardless of the patient's risk factor status at randomization, are presented in Table 2. One year of therapy with XENICAL resulted in relative improvement in several risk factors.

Table 2 **Mean Change in Risk Factors From Randomization Following 1-Year Treatment* Population as a Whole**

Risk Factor	XENICAL 120 mg†	Placebo†
Metabolic:		
Total Cholesterol	-2.0%	+5.0%
LDL-Cholesterol	-4.0%	+5.0%
HDL-Cholesterol	+9.3%	+12.8%
LDL/HDL	-0.37	-0.20
Triglycerides	+1.34%	+2.9%
Fasting Glucose, mmol/L	-0.04	+0.0
Fasting Insulin, pmol/L	-6.7	+5.2
Cardiovascular:		
Systolic Blood Pressure, mm Hg	-1.01	+0.58
Diastolic Blood Pressure, mm Hg	-1.19	+0.46
Anthropometric:		
Waist Circumference, cm	-6.45	-4.04
Hip Circumference, cm	-5.31	-2.96

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

† Intent-to-treat population at week 52, observed data based on pooled data from 5 studies

Population With Abnormal Risk Factors at Randomization

The changes from randomization following 1-year treatment in the population with abnormal lipid levels (LDL ≥ 130 mg/dL, LDL/HDL ≥ 3.5, HDL <35 mg/dL) were greater for XENICAL compared to placebo with respect to LDL-cholesterol (-7.83% vs +1.14%) and the LDL/HDL ratio (-0.64 vs -0.46). HDL increased in the placebo group by 20.1% and in the XENICAL group by 18.8%. In the population with abnormal blood pressure at baseline (systolic BP ≥ 140 mm Hg), the change in SBP from randomization to 1 year was greater for XENICAL (-10.89 mm Hg) than placebo (-5.07 mm Hg). For patients with a diastolic blood pressure ≥90 mm Hg, XENICAL patients decreased by -7.9 mm Hg while the placebo patients decreased by -5.5 mm Hg. Fasting insulin decreased more for XENICAL than placebo (-39 vs -16 pmol/L) from randomization to 1 year in the population with abnormal baseline values (≥120 pmol/L). A greater reduction in waist circumference for XENICAL vs placebo (-7.29 vs -4.53 cm) was observed in the population with abnormal baseline values (≥100 cm).

Effect on Weight Regain

Three studies were designed to evaluate the effects of XENICAL compared to placebo in reducing weight regain after a previous weight loss achieved following either diet alone (one study, 14302) or prior treatment with XENICAL (two studies, 14119C and 14185). The diet utilized during the 1-year weight regain portion of the studies was a weight-

maintenance diet, rather than a weight-loss diet, and patients received less nutritional counseling than patients in weight-loss studies. For studies 14119C and 14185, patients' previous weight loss was due to 1 year of treatment with XENICAL in conjunction with a mildly hypocaloric diet. Study 14302 was conducted to evaluate the effects of 1 year of treatment with XENICAL on weight regain in patients who had lost 8% or more of their body weight in the previous 6 months on diet alone.

In study 14119C, patients treated with placebo regained 52% of the weight they had previously lost while the patients treated with XENICAL regained 26% of the weight they had previously lost ($p<0.001$). In study 14185, patients treated with placebo regained 63% of the weight they had previously lost while the patients treated with XENICAL regained 35% of the weight they had lost ($p<0.001$). In study 14302, patients treated with placebo regained 53% of the weight they had previously lost while the patients treated with XENICAL regained 32% of the weight that they had lost ($p<0.001$).

Two-year Results: Long-term Weight Control and Risk Factors

The treatment effects of XENICAL were examined for 2 years in four of the five 1-year weight management clinical studies previously discussed (see Table 1). At the end of year 1, the patients' diets were reviewed and changed where necessary. The diet prescribed in the second year was designed to maintain patient's current weight. XENICAL was shown to be more effective than placebo in long-term weight control in four large, multicenter, 2-year double-blind, placebo-controlled studies.

Pooled data from four clinical studies indicate that 40% of all patients treated with 120 mg three times a day of XENICAL and 24% of patients treated with placebo who completed 2 years of the same therapy had ≥5% loss of body weight from randomization. Pooled data from four clinical studies indicate that the relative weight loss advantage between XENICAL 120 mg three times a day and placebo treatment groups was the same after 2 years as for 1 year, indicating that the pharmacologic advantage of XENICAL was maintained over 2 years. In the same studies cited in the **One-year Results** (see Table 1), the percentages of patients achieving a ≥5% and ≥10% weight loss after 2 years are shown in Table 3.

Table 3 Percentage of Patients Losing ≥5% and ≥10% of Body Weight From Randomization After 2-Year Treatment*

Intent-to-Treat Population†									
	≥5% Weight Loss					≥10% Weight Loss			
Study No.	XENICAL	n	Placebo	n	p-value	XENICAL	n	Placebo	n	p-value
14119C	45.1%	133	23.6%	123	<0.001	24.8%	133	6.5%	123	<0.001
14149	43.3%	178	27.2%	158	0.002	18.0%	178	9.5%	158	0.025
14161‡	25.0%	148	15.0%	113	0.049	16.9%	148	3.5%	113	0.001
14185	34.0%	147	27.9%	122	0.279	17.7%	147	11.5%	122	0.154

The diet utilized during year 2 was designed for weight maintenance and not weight loss.

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

† Last observation carried forward

‡ All studies, with the exception of 14161 were conducted at centers specializing in treating obesity or complications of obesity. Study 14161 was conducted with primary care physicians.

The relative changes in risk factors associated with obesity following 2 years of therapy were also assessed in the population as a whole and the population with abnormal risk factors at randomization.

Population as a Whole

The relative differences in risk factors between treatment with XENICAL and placebo were similar to the results following 1 year of therapy for total cholesterol, LDL-cholesterol, LDL/HDL ratio, triglycerides, fasting glucose, fasting insulin, diastolic blood pressure, waist circumference, and hip circumference. The relative differences between treatment groups for HDL cholesterol and systolic blood pressure were less than that observed in the year one results.

Population With Abnormal Risk Factors at Randomization

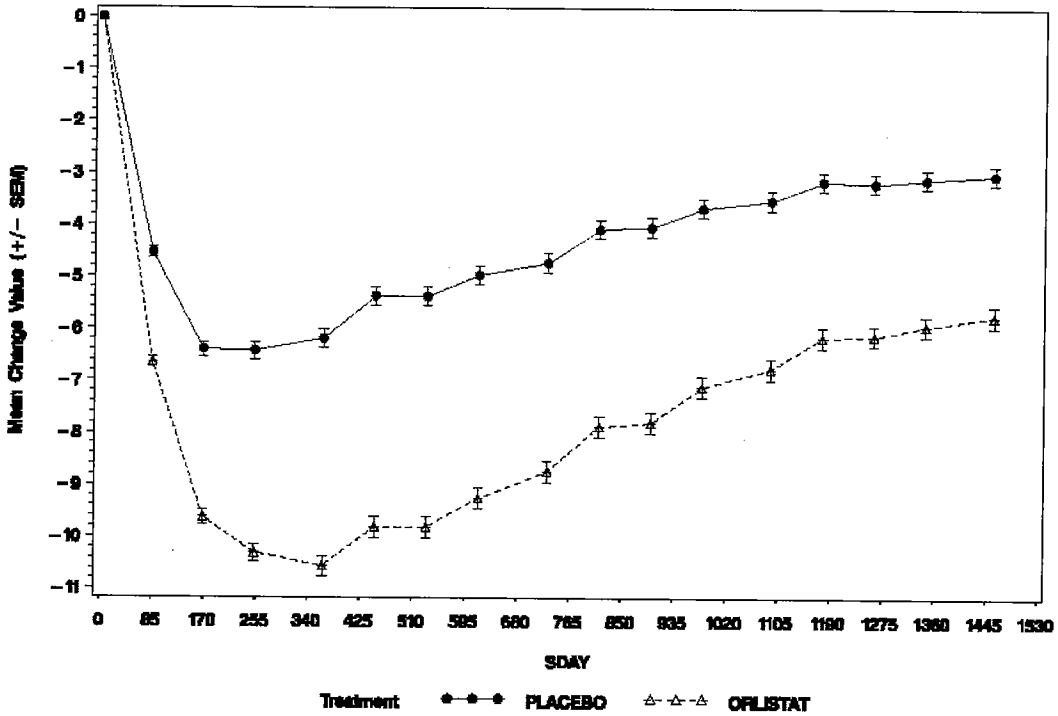
The relative differences in risk factors between treatment with XENICAL and placebo were similar to the results following 1 year of therapy for LDL- and HDL-cholesterol, triglycerides, fasting insulin, diastolic blood pressure, and waist circumference. The relative differences between treatment groups for LDL/HDL ratio and isolated systolic blood pressure were less than that observed in the year one results.

Four-Year Results: Long-term Weight Control and Risk Factors

In the 4-year double-blind, placebo-controlled XENDOS study, the effects of orlistat in delaying the onset of type 2 diabetes and on body weight were compared to placebo in 3304 obese patients who had either normal or impaired glucose tolerance at baseline. Thirty-four percent of the 1655 patients who were randomized to the placebo group and 52% of the 1649 patients who were randomized to the orlistat group completed the 4-year study.

At the end of the study, the mean percent weight loss in the placebo group was -2.75% compared with -5.17% in the orlistat group ($p<0.001$) (see Figure 1). Forty-five percent of the placebo patients and 73% of the orlistat patients lost =5% of their baseline body weight, and 21% of the placebo patients and 41% of the orlistat patients lost =10% of their baseline body weight following the first year of treatment. Following 4 years of treatment, 28% of the placebo patients and 45% of the orlistat patients lost =5% of their baseline body weight and 10% of the placebo patients and 21% of the orlistat patients lost =10% of their baseline body weight.

Figure 1 **Mean Change from Baseline Body Weight (Kgs) Over Time**



The relative changes from baseline in risk factors associated with obesity following 4 years of therapy were assessed in the XENDOS study population (see Table 4).

Table 4 **Mean Change in Risk Factors From Randomization Following 4-Years Treatment***

Risk Factor	XENICAL 120 mg†	Placebo†
Metabolic:		
Total Cholesterol	-7.02%	-2.03%
LDL-Cholesterol	-11.66%	-3.85%
HDL-Cholesterol	+5.92%	+7.01%
LDL/HDL	-0.53	-0.33
Triglycerides	+3.64%	+1.30
Fasting Glucose, mmol/L	+0.12	+0.23
Fasting Insulin, pmol/L	-24.93	-15.71
Cardiovascular:		
Systolic Blood Pressure, mm Hg	-4.12	-2.60
Diastolic Blood Pressure, mm Hg	-1.93	-0.87
Anthropometric:		
Waist Circumference, cm	-5.78	-3.99

*Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet
†Intent-to-treat population

Study of Patients With Type 2 Diabetes

A 1-year double-blind, placebo-controlled study in type 2 diabetics (N=321) stabilized on sulfonylureas was conducted. Thirty percent of patients treated with XENICAL achieved at least a 5% or greater reduction in body weight from randomization compared to 13% of the placebo-treated patients ($p<0.001$). Table 5 describes the changes over 1 year of treatment with XENICAL compared to placebo, in sulfonylurea usage and dose reduction as well as in hemoglobin HbA1c, fasting glucose, and insulin.

Table 5 **Mean Changes in Body Weight and Glycemic Control From Randomization Following 1-Year Treatment in Patients With Type 2 Diabetes**

	XENICAL 120 mg* (n=162)	Placebo* (n=159)	Statistical Significance
% patients who discontinued dose of oral sulfonylurea	11.7%	7.5%	†
% patients who decreased dose of oral sulfonylurea	31.5%	21.4%	
Average reduction in sulfonylurea medication dose	-22.8%	-9.1%	†
Body weight change (lbs)	-8.9	-4.2	†
HbA1c	-0.18%	+0.28%	†
Fasting glucose, mmol/L	-0.02	+0.54	†
Fasting insulin, pmol/L	-19.68	-18.02	ns

Statistical significance based on intent-to-treat population, last observation carried forward.

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

† Statistically significant ($p \leq 0.05$) based on intent-to-treat, last observation carried forward

ns nonsignificant, $p>0.05$

In addition, XENICAL (n=162) compared to placebo (n=159) was associated with significant lowering for total cholesterol (-1.0% vs +9.0%, $p \leq 0.05$), LDL-cholesterol (-3.0% vs +10.0%, $p \leq 0.05$), LDL/HDL ratio (-0.26 vs -0.02, $p \leq 0.05$) and triglycerides (+2.54% vs +16.2%, $p \leq 0.05$), respectively. For HDL cholesterol, there was a +6.49% increase on XENICAL and +8.6% increase on placebo, $p>0.05$. Systolic blood pressure increased by +0.61 mm Hg on XENICAL and increased by +4.33 mm Hg on placebo, $p>0.05$. Diastolic blood pressure decreased by -0.47 mm Hg for XENICAL and by -0.5 mm Hg for placebo, $p>0.05$.

Glucose Tolerance in Obese Patients

Two-year studies that included oral glucose tolerance tests were conducted in obese patients not previously diagnosed or treated for type 2 diabetes and whose baseline oral glucose tolerance test (OGTT) status at randomization was either normal, impaired, or diabetic.

The progression from a normal OGTT at randomization to a diabetic or impaired OGTT following 2 years of treatment with XENICAL (n=251) or placebo (n=207) were compared. Following treatment with XENICAL, 0.0% and 7.2% of the patients progressed from normal to diabetic and normal to impaired, respectively, compared to 1.9% and 12.6% of the placebo treatment group, respectively.

In patients found to have an impaired OGTT at randomization, the percent of patients improving to normal or deteriorating to diabetic status following 1 and 2 years of treatment with XENICAL compared to placebo are presented. After 1 year of treatment, 45.8% of the placebo patients and 73% of the XENICAL patients had a normal oral glucose tolerance test while 10.4% of the placebo patients and 2.6% of the XENICAL patients became diabetic. After 2 years of treatment, 50% of the placebo patients and 71.7% of the XENICAL patients had a normal oral glucose tolerance test while 7.5% of placebo patients were found to be diabetic and 1.7% of XENICAL patients were found to be diabetic after treatment.

Onset of Type 2 Diabetes in Obese Patients

In the XENDOS trial, in the overall population, orlistat delayed the onset of type 2 diabetes such that at the end of four years of treatment the cumulative incidence rate of diabetes was 8.3% for the placebo group compared to 5.5% for the orlistat group, p=0.01 (see Table 6). This finding was driven by a statistically-significant reduction in the incidence of developing type 2 diabetes in those patients who had impaired glucose tolerance at baseline (Table 6 and Figure 2). Orlistat did not reduce the risk for the development of diabetes in patients with normal glucose tolerance at baseline.

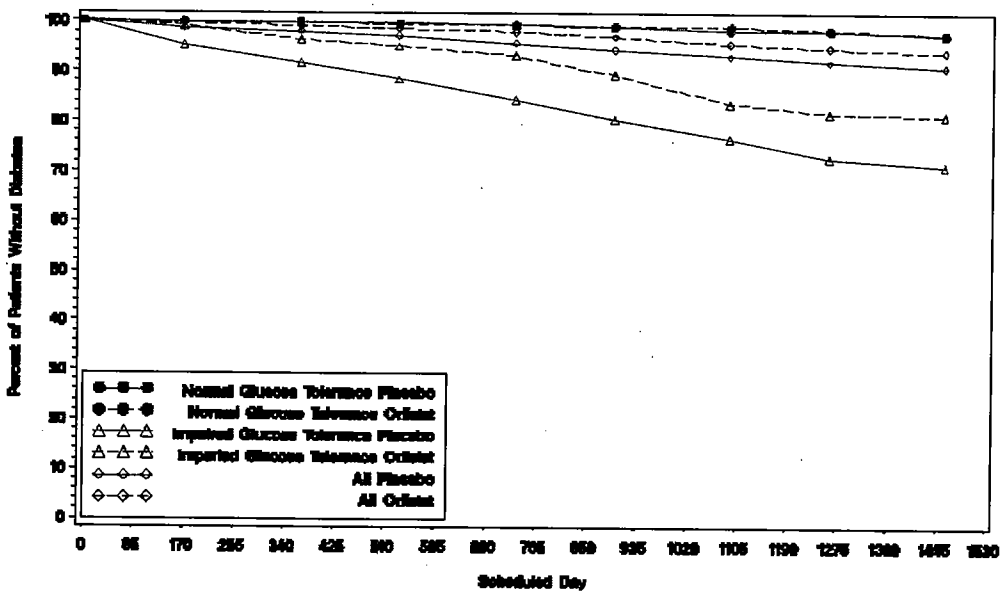
The effect of XENICAL to delay the onset of type 2 diabetes in obese patients with IGT is presumably due to weight loss, and not to any independent effects of the drug on glucose or insulin metabolism. The effect of orlistat on weight loss is adjunctive to diet and exercise.

Table 6 Incidence Rate of Diabetes at Year 4 by OGTT Status at Baseline*

OGTT at baseline	**Normal**		**Impaired**		**All**	
Treatment	Placebo	Orlistat	Placebo	Orlistat	Placebo	Orlistat
Number of patients*	1148	1235	324	337	1472	1572
# pts developing diabetes	16	21	62	48	78	69
Life table rate†	2.1%	1.7%	27.2%	18.7%	8.3%	5.5%
Observed percent	1.4%	1.7%	19.1%	14.2%	5.3%	4.4%
Absolute risk reduction						
Life table	0.4%		8.5%		2.8%	
Observed	-0.3%		4.9%		0.9%	
Relative risk reduction††	8%		42%		34%	
p-value	0.79		<0.01		0.01	

*Based on patients with a baseline and at least one follow-up OGTT measurement
†Rate adjusted for dropouts
†† Computed as (1- hazard ratio)

Figure 2 Percentage of Patients Without Diabetes Over Time



Pediatric Clinical Studies

The effects of XENICAL on body mass index (BMI) and weight loss were assessed in a 54-week multicenter, double-blind, placebo-controlled study in 539 obese adolescents (357 receiving XENICAL 120 mg three times a day, 182 receiving placebo), aged 12 to 16 years. All study participants had a baseline BMI that was 2 units greater than the US weighted mean for the 95th percentile based on age and gender. Body mass index was the primary efficacy parameter because it takes into account changes in height and body weight, which occur in growing children.

During the study, all patients were instructed to take a multivitamin containing fat-soluble vitamins at least 2 hours before or after ingestion of XENICAL. Patients were also maintained on a well-balanced, reduced-calorie diet that was intended to provide 30% of calories from fat. In addition, all patients were placed on a behavior modification program and offered exercise counseling.

Approximately 65% of patients in each treatment group completed the study.

Following one year of treatment, BMI decreased by an average of 0.55 kg/m^2 in the XENICAL-treated patients and increased by an average of 0.31 kg/m^2 in the placebo-treated patients ($p=0.001$).

The percentages of patients achieving ≥5% and ≥10% reduction in BMI and body weight after 52 weeks of treatment for the intent-to-treat population are presented in Table 7.

Xenical® (orlistat)
Capsules 120 mg

Item 2

Table 7 **Percentages of Patients with ≥5% and ≥10% Decrease in Body Mass Index and Body Weight After 1-Year Treatment* (Protocol NM16189)**

	Intent-to-Treat Population†							
	≥5% Decrease				≥10% Decrease			
	XENICAL	n	Placebo	n	XENICAL	n	Placebo	n
BMI	26.5%	347	15.7%	178	13.3%	347	4.5%	178
Body Weight	19.0%	348	11.7%	180	9.5%	348	3.3%	180

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

† Last observation carried forward

INDICATIONS AND USAGE

XENICAL is indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. XENICAL is also indicated to reduce the risk for weight regain after prior weight loss. XENICAL is indicated for obese patients with an initial body mass index (BMI) ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of other risk factors (eg, hypertension, diabetes, dyslipidemia).

Table 8 illustrates body mass index (BMI) according to a variety of weights and heights. The BMI is calculated by dividing weight in kilograms by height in meters squared. For example, a person who weighs 180 lbs and is 5'5" would have a BMI of 30.

Table 8 **Body Mass Index (BMI), kg/m^2***

HEIGHT (ft/in)	WEIGHT (lb)																				
	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280	290	300	310	320
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	47	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

* Conversion Factors:
Weight in lbs ÷ 2.2 = weight in kilograms (kg)
Height in inches × 0.0254 = height in meters (m)
1 foot = 12 inches

CONTRAINDICATIONS

XENICAL is contraindicated in patients with chronic malabsorption syndrome or cholestasis, and in patients with known hypersensitivity to XENICAL or to any component of this product.

WARNINGS

Miscellaneous

Organic causes of obesity (eg, hypothyroidism) should be excluded before prescribing XENICAL.

Preliminary data from a XENICAL and cyclosporine drug interaction study indicate a reduction in cyclosporine plasma levels when XENICAL was coadministered with cyclosporine. Therefore, XENICAL and cyclosporine should not be coadministered. To reduce the chance of a drug-drug interaction, cyclosporine should be taken at least 2 hours before or after XENICAL in patients taking both drugs. In addition, in those patients whose cyclosporine levels are being measured, more frequent monitoring should be considered.

PRECAUTIONS

General

Patients should be advised to adhere to dietary guidelines (see DOSAGE AND ADMINISTRATION). Gastrointestinal events (see ADVERSE REACTIONS) may increase when XENICAL is taken with a diet high in fat (>30% total daily calories from fat). The daily intake of fat should be distributed over three main meals. If XENICAL is taken with any one meal very high in fat, the possibility of gastrointestinal effects increases.

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 (see DOSAGE AND ADMINISTRATION). In addition, the levels of vitamin D and beta-carotene may be low in obese patients compared with non-obese subjects. The supplement should be taken once a day at least 2 hours before or after the administration of XENICAL, such as at bedtime.

Table 9 illustrates the percentage of adult patients on XENICAL and placebo who developed a low vitamin level on two or more consecutive visits during 1 and 2 years of therapy in studies in which patients were not previously receiving vitamin supplementation.

Table 9 **Incidence of Low Vitamin Values on Two or More Consecutive Visits (Nonsupplemented Adult Patients With Normal Baseline Values - First and Second Year)**

	Placebo*	XENICAL*
Vitamin A	1.0%	2.2%
Vitamin D	6.6%	12.0%
Vitamin E	1.0%	5.8%
Beta-carotene	1.7%	6.1%

* Treatment designates placebo plus diet or XENICAL plus diet

Table 10 illustrates the percentage of adolescent patients on XENICAL and placebo who developed a low vitamin level on two or more consecutive visits during the 1-year study.

Table 10 **Incidence of Low Vitamin Values on Two or More Consecutive Visits (Pediatric Patients With Normal Baseline Values*)**

	Placebo†	XENICAL†
Vitamin A	0.0%	0.0%
Vitamin D	0.7%	1.4%
Vitamin E	0.0%	0.0%
Beta-carotene	0.8%	1.5%

* All patients were treated with vitamin supplementation throughout the course of the study

† Treatment designates placebo plus diet or XENICAL plus diet

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 (eg, 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.

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 (eg, approximately 3 glasses of wine) did not result in alteration of alcohol pharmacokinetics, orlistat pharmacodynamics (fecal fat excretion), or systemic exposure to orlistat.

Cyclosporine

Preliminary data from a XENICAL and cyclosporine drug interaction study indicate a reduction in cyclosporine plasma levels when XENICAL was coadministered with cyclosporine (see WARNINGS).

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.

In a 2-way crossover study of 24 normal-weight, mildly hypercholesterolemic patients receiving XENICAL 120 mg three times a day for 6 days, XENICAL did not affect the pharmacokinetics of pravastatin.

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 an 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/m^2) 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/m^2) 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/m^2) 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 have been evaluated in obese adolescent patients aged 12 to 16 years. Use of XENICAL in this age group is supported by evidence from adequate and well-controlled studies of XENICAL in adults with additional data from a 54-week efficacy and safety study and a 21-day mineral balance study in obese adolescent patients aged 12 to 16 years. Patients treated with XENICAL had a mean reduction in BMI of 0.55 kg/m^2 compared with an average increase of 0.31 kg/m^2 in placebo-treated patients (p=0.001). In both adolescent studies, adverse effects were generally similar to those described in adults and included fatty/oily stool, oily spotting, and oily evacuation. In a subgroup of 152 orlistat and 77 placebo patients from the 54-week study, changes in body composition measured by DEXA were similar in both treatment groups with the exception of fat mass, which was significantly reduced in patients treated with XENICAL compared to patients treated with placebo (-2.5 kg vs -0.6 kg, p=0.033). Because XENICAL can interfere with the absorption of fat-soluble vitamins, all patients should take a daily multivitamin that contains vitamins A, D, E, K, and beta-carotene. The supplement should be taken at least 2 hours before or after XENICAL (see CLINICAL PHARMACOLOGY: Other Short-term Studies; CLINICAL STUDIES: Pediatric Clinical Studies; ADVERSE REACTIONS: Pediatric Patients). XENICAL has not been studied in pediatric patients below the age of 12 years.

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 the seven double-blind, placebo-controlled clinical trials and are primarily a manifestation of the mechanism of action. (Commonly observed is defined as an incidence of ≥5% and an incidence in the XENICAL 120 mg group that is at least twice that of placebo.)

Table 11 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 ≥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.

Table 12 **Other Treatment-Emergent Adverse Events From Seven Placebo-Controlled Clinical Trials**

Body System/Adverse Event	Year 1 XENICAL* % Patients (N=1913)	Year 1 Placebo* % Patients (N=1466)	Year 2 XENICAL* % Patients (N=613)	Year 2 Placebo* % Patients (N=524)
Gastrointestinal System				
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	–	–
Respiratory System				
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	–	–
Musculoskeletal System				
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
Central Nervous System				
Headache	30.6	27.6	–	–
Dizziness	5.2	5.0	–	–
Body as a Whole				
Fatigue	7.2	6.4	3.1	1.7
Sleep Disorder	3.9	3.3	–	–
Skin & Appendages				
Rash	4.3	4.0	–	–
Dry Skin	2.1	1.4	–	–
Reproductive, Female				
Menstrual Irregularity	9.8	7.5	–	–
Vaginitis	3.8	3.6	2.6	1.9
Urinary System				
Urinary Tract Infection	7.5	7.3	5.9	4.8
Psychiatric Disorder				
Psychiatric Anxiety	4.7	2.9	2.8	2.1
Depression	–	–	3.4	2.5
Hearing & Vestibular Disorders				
Otitis	4.3	3.4	2.9	2.5
Cardiovascular Disorders				
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 ≥2% and greater than placebo

In the 4-year XENDOS study, the general pattern of adverse events was similar to that reported for the 1- and 2-year studies with the total incidence of gastrointestinal-related adverse events occurring in year 1 decreasing each year over the 4-year period.

Other Clinical Studies or Postmarketing Surveillance

Rare cases of hypersensitivity have been reported with the use of XENICAL. Signs and symptoms have included pruritus, rash, urticaria, angioedema, bronchospasm and anaphylaxis. Very rare cases of bullous eruption, increase in transaminases and in alkaline phosphatase, and exceptional cases of hepatitis that may be serious have been reported. No causal relationship or physiopathological mechanism between hepatitis and orlistat therapy has been established. Reports of decreased prothrombin, increased INR and unbalanced anticoagulant treatment resulting in change of hemostatic parameters have been reported in patients treated concomitantly with orlistat and anticoagulants.

In clinical trials in obese diabetic patients, hypoglycemia and abdominal distension were also observed.

Preliminary data from a XENICAL and cyclosporine drug interaction study indicate a reduction in cyclosporine plasma levels when XENICAL was coadministered with cyclosporine (see WARNINGS).

Pediatric Patients

In clinical trials with XENICAL in adolescent patients ages 12 to 16 years, the profile of adverse reactions was generally similar to that observed in adults.

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 (see PRECAUTIONS:

General). 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 4 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.

XENICAL should not be used after the given expiration date.

Distributed by:

Roche Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

27898887

Revised: January 2005

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-766/ S-021

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-766/S-021 **CBE-0 SUPPLEMENT**

Hoffman-LaRoche, Inc.
Attention: Margaret J. Jack
Program Director
340 Kingsland Street
Nutley, New Jersey, 07110-1199

Dear Ms. Jack:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Xenical (orlistat) Capsules, 120 mg
NDA Number:	20-766
Supplement number:	-021
Date of supplement:	March 3, 2005
Date of receipt:	March 4, 2005

This supplemental application proposes labeling changes to the ADVERSE REACTIONS section of the label in the subsection entitled Other Clinical Studies or Postmarketing Surveillance.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 3, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 4, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/ Courier/Overnight Mail:

Center for Drug Evaluation and Research

Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Document Room, Room 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6381.

Sincerely,

{See appended electronic signature page}

Oluchi Elekwachi, Pharm.D., M.P.H.,
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Oluchi Elekwachi
4/4/05 10:00:24 AM

Division of Metabolic and Endocrine Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: N20-766/ S-021

Name of Drug: Xenical (Orlistat) Capsules 120 mg

Applicant: Hoffman LaRoche, Inc.

Material Reviewed: Package Insert (PI), Final Printed Labeling (FPL)

Submission Date(s): March 3, 2005

Receipt Date(s): March 4, 2005

Background and Summary

XENICAL (orlistat) is a lipase inhibitor for obesity management that acts by inhibiting the absorption of dietary fats. This Changes Being Effected (CBE-0) supplemental application proposes labeling changes to the ADVERSE REACTIONS section of the label in the subsection entitled Other Clinical Studies or Postmarketing Surveillance.

Review

The PI (Identifier 27898887 Revised: January 2005) was compared to the currently approved version of the PI, Approved with Supplement 19 on October 22, 2004 (No Identifier or Revision Date). Because the FA labeling for Supplement 19 was not acknowledged and retained at the time of this submission, it will be superceded by the labeling in this supplement.

Roche has made the following acceptable changes to the label:

- The section located directly under the **Storage Conditions** section contains the following editorial revisions
    - Identifier 27898863 has been changed to 27898887
    - The Revision date has been changed from October 2004 to January 2005
    - "Copyright. 1999-2004 by Roche Laboratories Inc. All rights reserved". Has been changed to "Copyright. 1999-2005 by Roche Laboratories Inc. All rights reserved"

Roche proposes to change the **Other Clinical Studies or Postmarketing Surveillance** subsection of the **ADVERSE REACTIONS** section of the label.

This subsection of the label is being changed from:

"Rare cases of hypersensitivity have been reported with the use of XENICAL. Signs and symptoms have included pruritus, rash, urticaria, angioedema, and anaphylaxis.

Preliminary data from a XENICAL and cyclosporine drug interaction study indicate a reduction in cyclosporine plasma levels when XENICAL was coadministered with cyclosporine (see WARNINGS)."

This subsection has been changed to:

"Rare cases of hypersensitivity have been reported with the use of XENICAL. Signs and symptoms have included pruritus, rash, urticaria, angioedema, bronchospasm and anaphylaxis. Very rare cases of bullous eruption, increase in transaminases and in alkaline phosphatase, and exceptional cases of hepatitis that may be serious have been reported. No causal relationship or physiopathological mechanism between hepatitis and orlistat therapy has been established. Reports of decreased prothrombin, increased INR and unbalanced anticoagulant treatment resulting in change of hemostatic parameters have been reported in patients treated concomitantly with orlistat and anticoagulants. In clinical trials in obese diabetic patients, hypoglycemia and abdominal distension were also observed.

Preliminary data from a XENICAL and cyclosporine drug interaction study indicate a reduction in cyclosporine plasma levels when XENICAL was coadministered with cyclosporine (see WARNINGS)."

This change has been found acceptable by Dr. Eric Colman, Medical Team Leader on September 1, 2005.

Conclusions

Issue an approval letter with labeling attached electronically.
The currently approved PI contains the Identifier 27898887 and a January 2005 revision date.

_____
Oluchi Elekwachi, PharmD, MPH
Regulatory Project Manager

Supervisory Comment/Concurrence:

Kati Johnson, RPh
Chief, Project Management Staff

Drafted: OUE 8/26/05
Revised/Initialed: KJohnson 09.01.2005
Finalized:09.01.2005
Filename: S-021 LabRev.doc

CSO LABELING REVIEW

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Oluchi Elekwachi
9/1/2005 08:42:08 PM
CSO