

# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

***APPLICATION NUMBER:***

**NDA 20-766/S-009**

***Trade Name:*** Xenical Capsules

***Generic Name:*** Orlistat

***Sponsor:*** Hoffman LaRoche, Inc.

***Approval Date:*** November 12, 2001

# **CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

**20-766/S-009**

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# **CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

**20-766/ S-009**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 18-044/S-030

NDA 20-766/S-009

Hoffman-La Roche Inc.  
Attention: Christine Hoogmoed  
Associate, Drug Regulatory Affairs  
340 Kingsland Street  
Nutley, NJ 07110-1199

Dear Ms. Hoogmoed:

Please refer to your supplemental new drug applications dated May 11, 2001, received May 14, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rocaltrol® (calcitriol) Capsules 0.25 and 0.5 mcg and for Xenical® (orlistat) Capsules 120 mg, respectively.

These "Changes Being Effected in 30 days" supplemental new drug applications provide for the addition of a new market package (bulk market drum) and for the addition of an alternate contract packaging site that may be used to package and label the product in the bulk market drum.

We acknowledge receipt of your amendment dated October 26, 2001, containing draft drum labeling.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (drum labels submitted October 26, 2001). Your amendment indicated your intention to submit FPL to your next annual report. Please provide this labeling as described in the next paragraph.

Please submit the copies of FPL electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999), or submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be entitled "FPL for approved supplemental NDAs 18-044/S-030 and 20-766/S-009." Approval of these submissions by FDA is not required before the labeling is used.

NDA 18-044/S-030  
NDA 20-766/S009

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If you have any questions, call James Cross, Regulatory Project Manager, at 301-827-6381.

Sincerely,

*{See appended electronic signature page}*

Duu-Gong Wu, Ph.D.  
Deputy Director, DNDC II  
Office of New Drug Chemistry, for the  
Division of Metabolic and Endocrine Drug Products  
Center for Drug Evaluation and Research

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/s/

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Duu-gong Wu

11/12/01 04:33:39 PM

# **CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

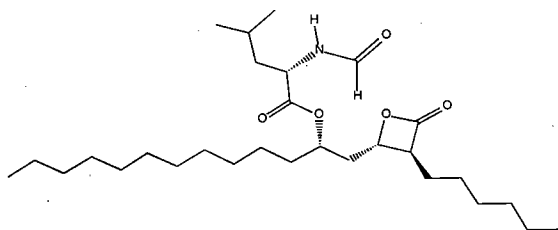
**20-766/S-009**

**APPROVED LABELING**

**XENICAL®****(orlistat)****CAPSULES****R<sub>x</sub> 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<sub>29</sub>H<sub>53</sub>NO<sub>5</sub>, 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<sub>a</sub> 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%.



## Pharmacokinetics

### Absorption

Systemic exposure to orlistat is minimal. Following oral dosing with 360 mg  $^{14}\text{C}$ -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  $0.02$   $\mu\text{M}$ ), 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  $^{14}\text{C}$ -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  $\beta$ -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  $^{14}\text{C}$ -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  $^{14}\text{C}$ -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  $\mu$ mole/24 hours and 40.4  $\mu$ mole/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.

### **CLINICAL STUDIES**

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 seven long-term (1- to 2-years duration) multicenter, double-blind, placebo-controlled clinical trials. During the first year of

therapy, weight loss and weight maintenance were assessed. 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 these 7 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  $\geq 5\%$  and  $\geq 10\%$  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  $\geq 5\%$  and  $\geq 10\%$  of Body Weight From Randomization After 1-Year Treatment\***

Intent-to-Treat Population†						
$\geq 5\%$ Weight Loss				$\geq 10\%$ 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†
<b>Metabolic:</b>		
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
<b>Cardiovascular:</b>		
Systolic Blood Pressure, mm Hg	-1.01	+0.58
Diastolic Blood Pressure, mm Hg	-1.19	+0.46
<b>Anthropometric:</b>		
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  $\geq$  130 mg/dL, LDL/HDL  $\geq$  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  $\geq$  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  $\geq$  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 ( $\geq$  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 ( $\geq$  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  $\geq 5\%$  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  $\geq 5\%$  and  $\geq 10\%$  weight loss after 2 years are shown in Table 3.

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

Study No.	Intent-to-Treat Population†					
	$\geq 5\%$ Weight Loss			$\geq 10\%$ Weight Loss		
	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.

### 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 4 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 4**      **Mean Changes in Body Weight and Glycemic Control From Randomization Following 1-Year Treatment in Patients With Type 2 Diabetes**

	<b>XENICAL 120 mg* (n=162)</b>	<b>Placebo* (n=159)</b>	<b>Statistical Significance</b>
% 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.

### **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 95<sup>th</sup> 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<sup>2</sup> in the XENICAL-treated patients and increased by an average of 0.31 kg/m<sup>2</sup> in the placebo-treated patients ( $p = 0.001$ ).

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

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

Intent-to-Treat Population†						
$\geq 5\%$ Decrease				$\geq 10\%$ 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)  $\geq 30$  kg/m<sup>2</sup> or  $\geq 27$  kg/m<sup>2</sup> in the presence of other risk factors (eg, hypertension, diabetes, dyslipidemia).

Table 6 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 6 Body Mass Index (BMI), kg/m<sup>2</sup>\***

		WEIGHT (lb)																				
HEIGHT (ft/in)		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  $\div$  2.2 = weight in kilograms (kg)

Height in inches  $\times$  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 7 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 7      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 8 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 8                      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.

### **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 (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.

### **Pravastatin**

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 ( $\text{mg}/\text{m}^2$ ) 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 ( $\text{mg}/\text{m}^2$ ) 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 ( $\text{mg}/\text{m}^2$ ) 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  $0.55 \text{ kg}/\text{m}^2$  compared with an average increase of  $0.31 \text{ kg}/\text{m}^2$  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 ( $-2.5 \text{ kg}$  vs  $-0.6 \text{ kg}$ ,  $p=0.033$ ). 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 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 9 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.

**Table 10 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 &amp; 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
<i>Hearing &amp; 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

### **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, 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).

### **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 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.**

XENICAL should not be used after the given expiration date.



**Pharmaceuticals**

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

XXXXXXXX

Revised: December 2003

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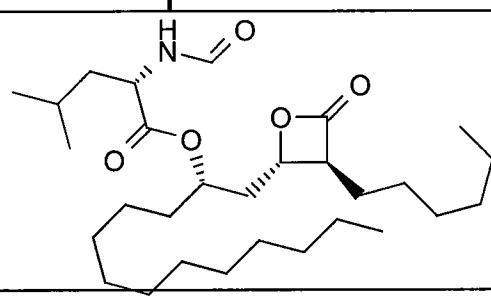


# **CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

**20-766/S-009**

**CHEMISTRY REVIEW(S)**

<b>CHEMIST'S REVIEW</b>	1. ORGANIZATION	2. NDA NUMBER
	DMEDP, HFD-510	<b>20-766</b>
3. NAME AND ADDRESS OF APPLICANT		4. SUPPLEMENT NUMBER, DATE
Hoffmann-La Roche Inc 340 Kingsland Street Nutley, NJ 07110-1199 (973) 235-5906		SCS-009, 5/11/01
5. NAME OF THE DRUG	6. NONPROPRIETARY NAME	UF date 11/14/01 CBE-30
Xenical	Orlistat	8. AMENDMENT, DATE
7. SUPPLEMENT PROVIDES FOR:		Labeling, 10/26/01
A new market package (bulk drum) and an alternate contact packaging site, _____		
9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND/NDA/DMF
Anti-obesity	Rx	NDA's 18225, 19488, 20005, 19979, 17581, 18164, 20067, 18044, 13263, 17533, 50722
12. DOSAGE FORM	13. POTENCY	
Capsule	120 mg	
14. CHEMICAL NAME AND STRUCTURE.		
(s)-2-formylamino-4-methylpentanoic acid (s)-1-[(2S,3S)-3-hexyl-4-oxo-2-oxetanylmethyl]-dodecyl ester		
15. COMMENTS		
<p>This bundled, CBE-30 supplement provides for a new market package (bulk drum, _____) and for an alternate contact packaging site, _____ / Review for lead NDA 18-225/S-20 by Dr. Zimmerman in HFD-110 was completed 10/18/01, recommending approval. The 10/26/01 amendment provides revised labeling as per Dr. Zimmerman's instructions. Satisfactory EER for the packaging site was received 5/24/01. For specific chemistry comments, see Review notes.</p>		
16. CONCLUSION AND RECOMMENDATION		
From a chemistry viewpoint, satisfactory information has been provided. Issue <b>Approval</b> letter.		
17. REVIEWER NAME	18. REVIEWER SIGNATURE	19. DATE COMPLETED
Martin Haber, Ph.D.		November 5, 2001
DISTRIBUTION: ORIGINAL JACKET J. Cross M. Haber DIVISION FILE		

R/D Init by: Dr. Duu-Gong Wu, Team Leader Chemist

**B: Establishment Inspection Reports:**

NDA 20766/SCS-009

**Satisfactory**

01-AUG-2001

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

Page 1 of 1

Application:	NDA 20766/009	Priority:	1P	Org Code:	510
Stamp:	14-MAY-2001	Regulatory Due:	14-NOV-2001	Action Goal:	District Goal: 10-OCT-2001
Applicant:	HLR	Brand Name:	XENICAL(ORLISTAT) 120		
	340 KINGSLAND ST	Established Name:			
	NUTLEY, NJ 071101199	Generic Name:	ORLISTAT/TETRAHYDROLIPSTATIN		
		Dosage Form:	CAP (CAPSULE)		
		Strength:	120 MG		
FDA Contacts:	J. CROSS	(HFD-510)	301-480-8174	, Project Manager	
	M. HABER	(HFD-510)	301-827-6420	, Review Chemist	
	D. WU	(HFD-510)	301-827-6375	, Team Leader	

**Overall Recommendation:**

**ACCEPTABLE on 24-MAY-2001 by J. D AMBROGIO (HFD-324) 301-827-0062**

Establishment: / \_\_\_\_\_ / DMF No:  
/ \_\_\_\_\_ / AADA No:

Profile: CHG OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 23-MAY-2001  
Decision: ACCEPTABLE  
Reason: BASED ON PROFILE

Responsibilities: / \_\_\_\_\_ /

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

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Martin Haber  
11/5/01 04:44:44 PM  
CHEMIST

approval

Duu-gong Wu  
11/6/01 09:56:01 AM  
CHEMIST

# **CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**20-766/ S-009**

**ADMINISTRATIVE DOCUMENTS**  
**AND**  
**CORRESPONDENCE**

Unless we notify you within 60 days of our receipt date that the applications are not sufficiently complete to permit a substantive review, these applications will be filed under section 505(b) of the Act on July 13, 2001 in accordance with 21 CFR 314.101(a). If the applications are filed, the user fee goal date will be November 14, 2001.

---

Food and Drug Administration  
Rockville MD 20857

Please cite the application numbers listed above at the top of the first page of any communications concerning these applications. All communications concerning these supplemental applications should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolic and Endocrine Drug Products, HFD-510  
Attention: Division Document Room  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any questions regarding 18-044/S-030, please contact Randy Hedin, Regulatory Project Manager, at 301-827-6392. If you have any questions regarding 20-766/S-009, please call me at 301-480-8174.

Sincerely,

*{See appended electronic signature page}*

James T. Cross  
Regulatory Project Manager  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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

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James Cross

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