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Approval Package for:

APPLICATION NUMBER:

NDA 20-766/S-018

Trade Name: Xenical Capsules

Generic Name: orlistat

Sponsor: Hoffman-La Roche, Inc.

Approval Date: December 12, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-766/S-018

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-766/S-018

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-766/S-018

Hoffmann-La Roche, Inc.
Attention: Encarnacion Suarez, Pharm.D.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Ms. Suarez:

Please refer to your supplemental new drug application dated June 23, 2003, received June 24, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xenical (orlistat) Capsules.

This supplemental new drug application provides for revised labeling to provide for use of Xenical Capsules in the management of obesity in adolescent patients aged 12 to 16 years.

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

Since universal multivitamin supplementation in patients treated with Xenical appears to reduce the risk for developing low levels of some fat-soluble vitamins and beta-carotene, we request that you submit your position regarding the feasibility of co-packaging a multivitamin supplement with Xenical Capsules.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert, submitted June 23, 2003

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-766/S-018." Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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, Pharm.D., M.P.H. , 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: Package Insert

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
12/12/03 04:17:38 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-766/S-018

Approved Labeling

Roche

XENICAL®

(orlistat)

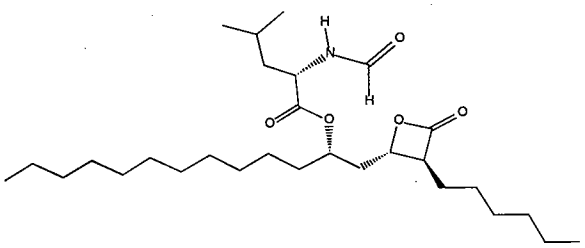
CAPSULES

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%.

Pharmacokinetics

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.

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 ≥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.

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

	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%, $p\leq0.05$), LDL-cholesterol (-3.0% vs +10.0%, $p\leq0.05$),

LDL/HDL ratio (-0.26 vs -0.02, p≤0.05) and triglycerides (+2.54% vs +16.2%, p≤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 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 5.

Table 5. 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 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^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 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 (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 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 9 Commonly Observed Adverse Events

	Year 1		Year 2	
Adverse Event	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 10 Other Treatment-Emergent Adverse Events From Seven Placebo-Controlled Clinical Trials

	Year 1		Year 2	
Body System/Adverse Event	**XENICAL* % Patients (N=1913)**	**Placebo* % Patients (N=1466)**	**XENICAL* % Patients (N=613)**	**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

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-766/S-018

Medical Review(s)

CLINICAL REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #: NDA 20-766 / S
Application Type:
Sponsor: Hoffmann-LaRoche, Inc
Proprietary Name: Orlistat
Pharmaceutical Category: Lipase Inhibitor
Route of Administration: Oral
Indication: Obesity management of adolescent patients aged 12 to 16 years
Dosage: 120mg tid with meals
Reviewer: Theresa Kehoe, MD
Date Review Completed: December 5, 2003

Chemistry Reviewer: N/A
Pharmacology Reviewer: N/A
Biopharmaceutics Reviewer: Wei Qiu, Ph.D.
Statistical Reviewer: Japo Choudhury, Ph.D.

REVIEW SUMMARY: In response to the Agency's Written Request, the efficacy and safety of orlistat in pediatric patients were assessed in two studies. The first was a 52-week, randomized (2:1), double-blind, placebo-controlled study of 539 obese adolescents (BMI > 97th percentile). The second was a 22-day, randomized (1:1) double-blind, placebo-controlled mineral balance study in 32 obese adolescents. Approximately 65% of the patients in each treatment group completed the one-year study and 94% of the subjects in each treatment group completed the mineral balance study. In the one-year study, orlistat use resulted in a statistically significant decrease in BMI when compared to placebo (-0.55 kg/m^2 vs. 0.31 kg/m^2; p=0.001). Overall, 26.5% of orlistat-treated patients and 15.7% of placebo-treated patients had a 5% reduction of their baseline BMI (p=0.005), while 13.3% of orlistat-treated patients and 4.5% of placebo-treated patients had a 10% reduction of their baseline BMI (p=0.002). Body weight and height increased in both groups, as one would expect in this growing population. However, the increase in body weight in the orlistat group (0.53 kg) was significantly less than the increase in the placebo group (3.1 kg) (p<0.001). Similar to results seen with BMI, 19% of orlistat-treated patients and 11% of placebo-treated patients had a 5% reduction in body weight, while 9.5% of orlistat-treated patients and 3.3% of placebo-treated patients had a 10% reduction in body weight. In previous studies of obese adults, approximately 60% of orlistat- treated patients and 31% of placebo-treated patients had a 5% reduction of their baseline body weight, while 27% of orlistat-treated patients and 11% of placebo-treated patients had a 10% reduction in body weight at one year of therapy. There was no statistical difference in the effect of orlistat on blood pressure, lipid parameters and glucose or insulin levels in this low-risk adolescent population. In the mineral balance study, all minerals, with the exception of iron, were maintained in positive balance in both the placebo and orlistat treatment groups. Both groups had decreases in mean iron levels, with larger decreased in the orlistat-treated subjects, a trend previously noted in mineral balance studies conducted in obese adult male subjects. There were no new safety signals noted from these studies in obese adolescent subjects. Similar to the adult population, gastrointestinal adverse events including fatty/oily stools were common in the orlistat-treated group. Fat soluble vitamin levels increased during the study in all subjects with larger increases in the placebo-treated subjects, probably because of universal daily multivitamin supplementation. In the adult orlistat studies, universal multivitamin supplementation was not implemented and the use of orlistat in these studies was associated with a lowering of some fat soluble vitamin levels. These findings suggest that the effects of orlistat use on fat soluble vitamins can be successfully ameliorated with concomitant multivitamin usage (i.e., 2 hours before or after taking orlistat).

OUTSTANDING ISSUE:

RECOMMENDED REGULATORY ACTION:
N drive location:

New clinical studies _____ **Clinical Hold** _____ **Study May Proceed**
NDA, Efficacy/Label supplement: _____ **Approvable** _____ **Not Approvable**
X **Approve**

SIGNATURES: **Medical Reviewer:** Theresa Kehoe, M.D. **Date:** December 5, 2003 .

Medical Team Leader: Eric Colman, M.D. **Date:** _____ .

CLINICAL REVIEW

Table of Contents

Clinical Review for NDA 20-766 / S-018

Executive Summary

I. Recommendations

A. Recommendation on Approvability
Approve

B. Recommendation on Phase 4 Studies and/or Risk Management Steps
Roche should strongly consider packaging the drug product with a multivitamin for use in the adolescent population.

II. Summary of Clinical Findings

A. Current Therapeutic Options for the Treatment of Obesity in Adolescents
The are currently no approved medical therapies for obesity management in adolescents.

B. Brief Overview of Clinical Program
Orlistat, trade name Xenical, chemical name tetrahydrolipistatin, is a pancreatic lipase inhibitor that acts by inhibiting the absorption of dietary fats. Orlistat was approved for the long-term treatment of obesity on 4/23/99, for adult patients with an initial body mass index (BMI) >30 kg/m^2 or > 27 kg/m^2 in the presence of other risk factors (e. g., hypertension, diabetes, dyslipidemia).

The efficacy and safety of orlistat in pediatric patients were assessed in two studies, as outlined in the Agency's 9 August 2000 Written Request. The first was a 52-week, randomized (2:1), double-blind, placebo-controlled study of 539 obese adolescents (BMI > 97^{th} percentile). The second was a 22-day, randomized (1:1) double-blind, placebo-controlled mineral balance study in 32 obese adolescents.

C. Efficacy
In the one-year trial, approximately 65% of the patients in each treatment group completed the study. Orlistat use in the adolescent population resulted in a statistically significant decrease in BMI (-0.55 kg/m^2) when compared to placebo (+0.31 kg/m^2) (p=0.001). Overall, 26.5% of orlistat-treated patients and 15.7% of placebo-treated patients had at least a 5% reduction of their baseline BMI (p=0.005), while 13.3% of orlistat-treated patients and 4.5% of placebo-treated patients had at least a 10% reduction of their baseline BMI (p=0.002). Body weight and height increased in both groups, as one would expect in this growing population. However, the increase in body weight in the orlistat group (0.53 kg) was significantly less than the increase in the placebo group (3.1 kg) (p=0.001). Similar to results seen with BMI, significantly more patients treated with

orlistat had at least 5% (19%) and 10% (9.5%) reductions in baseline body weight when compared with placebo-treated patients (11.7% and 3.3%, respectively ($p<0.05$ for both comparisons).).

In previously conducted studies of obese adults, approximately 60% of orlistat-treated patients and 31% of placebo-treated patients had at least a 5% reduction of their baseline body weight, while 27% of orlistat-treated patients and 11% of placebo-treated patients had at least a 10% reduction in body weight at one year of therapy.

Waist circumference decreased by an average of –2.6 cm in the orlistat group and by –0.6 cm in the placebo group ($p=0.008$). Hip circumference decreased by 1.3 cm in the orlistat-treated patients and increased by 0.1 cm in the placebo-treated subjects ($p=0.01$).

Fat mass and fat-free mass were directly measured by DEXA in a subgroup of 152 orlistat and 77 placebo subjects. At the end of treatment, the orlistat group had an average weight loss of -0.54 kg; whereas, the placebo subjects gained an average of 1.45 kg. Fat mass decreased by a mean of –2.4 kg in the orlistat group and increased by 0.38 kg in the placebo group ($p=0.03$).

There were no statistically significant differences between treatment groups in the changes in blood pressure, lipid parameters, and glucose or insulin levels in the low risk adolescent population.

In the 3-week mineral balance investigation, 94% of the subjects in each treatment group completed the study. Positive balance was maintained for calcium, magnesium, phosphorus, and zinc in both the orlistat and placebo groups, when measured on Day 22. Copper balance was –0.4 umol/24 hr in the orlistat group and 0.1 umol/24 hr in the placebo group. Both groups had decreases in mean iron balance (–32.9 µmol/24 hour in the placebo group versus –49.7 µmol/24 hour in the orlistat group). Negative iron balance was previously noted in mineral balance studies conducted in obese adult male subjects (–10.80 ± 11.10 in the placebo treated group, –18.90 ± 10.50 in the orlistat treated group). The etiology of the net loss of iron is unclear. There was no association between gender and iron balance. No significant differences were detected between treatment groups at Day 22 for either mean serum sodium (placebo, 141.7 mmol/L; orlistat, 142.4 mmol/L) or potassium (placebo, 4.1 mmol/L; orlistat, 4.1 mmol/L). There was also no significant difference detected in mean urine sodium (placebo, 108.2 mmol/L; orlistat, 113.4 mmol/L) or potassium (placebo, 60.0 mmol/L; orlistat, 43.0 mmol/L) levels.

D. Safety

In the two adolescent studies reviewed, a total of 373 subjects received at least one dose of orlistat and 198 subjects received at least one dose of placebo. Overall, 65% of orlistat-treated patients and 63% of placebo-treated patients completed the 52-week study and 94% of both orlistat and placebo treated subjects completed the 22 day inpatient study. The calculated compliance based on pill count was 73% in the orlistat treatment group and 72% in the placebo treatment group. There were no new safety signals noted from these studies in obese adolescent subjects. Similar to studies of orlistat in obese adults, gastrointestinal adverse events including fatty/oily stools were more common in the orlistat-treated group. Fat soluble vitamin levels

increased during the study in all subjects most likely because of the daily multivitamin supplementation. Vitamin levels were, however, lower in the orlistat- vs. the placebo-treated group. These differences were statistically significant for beta Carotene (3.00 µg/dl in the placebo group and 0.59 µg/dl in the orlistat group, p = 0.001) and Vitamin E (52.18 µmol/L in the placebo group and 11.92 µmol/Lin the orlistat group, p = 0.089). In the adults studies, universal multivitamin supplementation was not instituted and the use of orlistat was associated with a significant lowering of some plasma-fat soluble vitamin levels. These findings support the recommendation that all orlistat-treated patients take a daily supplement that contains all of the fat-soluble vitamins. There was no evidence that orlistat use had an impact on pulse, height, physical exam, sexual maturation, QTc interval or sex hormone levels.

E. Dosing

A single dose of orlistat was utilized in these clinical trials in obese adolescents. The dose used in these studies was the current marketed adult dose, 120mg t.i.d. The majority (88%) of subjects enrolled in these studies had a baseline body weight over 80kg, which is comparable to a normal weight adult population.

F. Special Populations

The efficacy and safety of orlistat use in the adolescent population correlates with that seen with orlistat use in the adult population. These adolescent studies enrolled subjects representing multiple races and spanned the adolescent ages from 12 – 16 years. Both male and female subjects were enrolled in these trials. Results were adequately analyzed for the effect of gender and none was found.

Clinical Review

I. Introduction and Background

I.A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Orlistat, trade name Xenical, chemical name tetrahydrolipistatin, is a pancreatic lipase inhibitor that acts by inhibiting the absorption of dietary fats. This supplemental marketing application is submitted in response to a written request for pediatric studies evaluating the use of the adult orlistat dose regimen (120mg three times a day) in adolescent obesity management.

I.B. State of Armamentarium for Indication(s)

Orlistat is the only lipase inhibitor that is approved for the long-term treatment of obesity. Sibutramine (Meridia) was approved for weight loss in 1997. There are no products currently approved for obesity management in adolescents.

I.C. Important Milestones in Product Development

Orlistat was approved for the long-term treatment of obesity on 4/23/99, 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 (e. g., hypertension, diabetes, dyslipidemia). [redacted] The sponsor received a written request for pediatric studies for obesity management from the FDA in a letter dated August 9, 2000.

I.D. Other Relevant Information

[redacted]

I.E. Important Issues with Pharmacologically Related Agents

Orlistat is the only lipase inhibitor that is approved for the long-term treatment of obesity.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

The chemistry review of orlistat was completed with the original NDA submission. There are no new chemistry issues with this submission. 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 animal pharmacology and toxicology review was conducted for the original marketing application. Decreased concentrations of the fat soluble vitamins, vitamin D and vitamin E, and beta carotene have been observed in animal studies. No new pharmacology and toxicology studies were submitted with this application.

The statistical review of this supplement was completed by Dr. Choudhury. The analyses performed agreed with that of the sponsor. Please see Dr. Choudhury's review for complete details.

III. Human Pharmacokinetics and Pharmacodynamics

Pharmacokinetics and pharmacodynamic studies in adults were reviewed in the original marketing application.

III.A. Pharmacokinetics

The vast majority (> 99%) of orally ingested orlistat is excreted unchanged in the feces. The small amount that is absorbed undergoes extensive first pass metabolism. New pharmacokinetic data in this submission relate to the evaluation of orlistat and an interaction with metformin, which showed no interaction. Please see Dr. Qiu's review for further details.

III.B. Pharmacodynamics

Orlistat is a reversible inhibitor of gastrointestinal lipases: pancreatic lipase, gastric/ lingual lipase, and carboxyl ester lipase. In the gastrointestinal tract, the drug's site of action, orlistat inhibits absorption of dietary triglycerides. Sequestration of orlistat with unabsorbed triglycerides reduces cholesterol absorption. Orlistat also inhibits lipoprotein, hepatic, hormone sensitive, and diacylglycerol lipases, though its extremely low bioavailability precludes a clinically meaningful effect on these lipases. Decreased concentrations of the fat soluble vitamins, vitamin D and vitamin E, and beta carotene have been observed in prior clinical studies in overweight and obese adults.

IV. Description of Clinical Data and Sources

IV.A. Overall Data

The orlistat clinical development program for obese adolescent patients was undertaken to provide information on the safety and efficacy of orlistat in obese adolescent patients, as requested in the formal Written Request for pediatric studies dated August 9, 2000. This clinical development program was prospectively designed based on the extensive previous clinical experience in the adult population and after identifying and considering the potential differences between the two patient populations. Over 7000 subjects participated in the original global development program for orlistat. The phase 3 clinical program included 4,230 obese and overweight adult patients (body mass index (BMI) of 28 kg/m2 to 43 kg/m2) in seven large-scale double-blind, placebo controlled trials lasting up to two years. There have now been close to one hundred controlled clinical trials in over 30,000 patients with studies of up to four years in duration.

The clinical studies in the adult population used body weight as a primary efficacy parameter. Since adolescent subjects are likely to still be growing, body mass index (BMI), which takes into account increases in height and the concomitant increases in lean body weight, rather than body weight alone was used as study entry criteria and the primary efficacy endpoint for the adolescent studies. Based on the mechanism of action of orlistat, other potential differences between the adult and adolescent patient populations including gastrointestinal pathology, diet, mineral balance, and the absorption of fat-soluble vitamins were considered and evaluated.

IV.B. Tables Listing the Clinical Trials

Orlistat Trials in Adolescent Obesity				
-		Subjects enrolled/completed	Duration	Endpoint
NM16189	total	539 (349)	54 weeks	BMI
	Orlistat120 tid	357 (232)		
	Placebo tid	182 (117)		
PP16203	total	32 (30)	22 days	Mineral balance
	Orlistat120 tid	16 (15)		
	Placebo tid	16 (15)		

IV.C. Postmarketing Experience

Orlistat has been on the market in the EU since July 1998 and in the US since April 1999. The total estimated exposure to orlistat up until January 2003 is approximately 16 million patient treatments. Information on any adverse event reported for children 17 years of age or younger was obtained from the sponsor's database, which includes events reported globally from health professionals, consumers, and literature reports. A total of eight adverse events, two of which were serious, have been reported in children less than 12 years of age. The two serious adverse events were mydriasis and accidental exposure, both of which were reported in a 3-year-old male who accidentally ingested orlistat. A total of 12 adverse events, two of which were serious, have been reported in children and adolescents between the ages of 12 and 16. The two serious adverse events included gastrointestinal disorder and drug interaction, both of which were reported by a 16-year-old female who was consuming Olestra-containing snacks while taking orlistat.

IV.D. Literature Review

A literature search for studies of orlistat in obese adolescents was conducted using the following databases:

. Two studies conducted in obese adolescents were identified. One was a 6-month study on the efficacy of orlistat in overweight adolescents with obesity-related co-morbid conditions conducted by The Division of Nutrition Research Coordination (NIDDK) at the National Institutes of Health (NIH). The second was a 12-week study conducted in 11 obese prepubertal children. The safety profile of orlistat in both of these studies was similar to that previously observed in the sponsor conducted clinical trials and no new events of clinical concern were reported.

V. Clinical Review Methods

V.A. How the Review was Conducted

This review focuses on study NM16189, which evaluated the safety and efficacy of orlistat use for obesity management in adolescent patients aged 12 to 16 years.

V.A. Overview of Materials Consulted in Review

This review was conducted utilizing data in the electronic submission of the NDA. All trials were conducted under IND 31,617.

V.B. Overview of Methods Used to Evaluate Data Quality and Integrity

The Division of Scientific Investigation (DSI) was not consulted for this supplemental NDA.

V.C. Were Trials Conducted in Accordance with Accepted Ethical Standards

All studies appear to have been conducted in accordance with FDA guidelines on "Good Clinical Practice" and the principles of the Declaration of Helsinki.

V.D. Evaluation of Financial Disclosure

Financial disclosure information was provided by the sponsor and reviewed by this reviewer. None of the investigators involved with trials NM16189 and PP16203 reported any financial interests.

VI. Integrated Review of Efficacy

VI.A. Brief Statement of Conclusions

Orlistat is effective for use in weight management in the adolescent population, ages 12 to 16 years. The observed weight loss effect is not as robust as what was seen in the adult population, but remains statistically significant.

VI.B. General Approach to Review of the Efficacy of the Drug

The pivotal trials requested in the pediatric written request are reviewed in depth in this review. Study NM16189 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of obese adolescents aged 12 to 16 years. Study PP16203 was an inpatient, single-center, double-blind, randomized, placebo-controlled, parallel-group, study in obese adolescents evaluating the effect of orlistat on the balance of selected minerals.

VI.C. Detailed Review of Trials by Indication

VI.C.1. Study NM16189: This was a multicenter, randomized, double-blind, placebo-controlled, 54-week study conducted in obese adolescent patients.

Objectives: The primary objectives of this study were:

1. To characterize the efficacy of orlistat administered daily (120 mg tid with meals) as an adjunct to diet in the treatment of obese pediatric patients.
2. To characterize the safety profile of orlistat administered daily (120 mg tid with meals) in obese pediatric patients, using the following endpoints: gastrointestinal tolerability, linear growth and Tanner pubertal stage assessment, bone mineral content, body composition (DEXA), fat-soluble vitamin, beta-carotene, parathyroid hormone, and serum calcium levels, and gall bladder and renal ultrasound

The secondary objective of this study was:

1. To characterize changes in obesity-related risk factors, including total cholesterol, LDL-cholesterol, HDL-cholesterol, LDL/HDL cholesterol ratio, triglycerides, systolic and diastolic blood pressure, waist circumference, and glucose and insulin responses to an oral glucose challenge

Study Design: This was a multicenter, randomized, double-blind, placebo-controlled, 54-week study conducted in obese adolescent patients. A 2-week placebo lead in period preceded the 52-weekdouble-blind treatment period. Patients received nutritional, behavior modification, and exercise counseling beginning with the placebo lead-in period. A hypocaloric diet was to be maintained and multivitamin supplementation was to be taken to all patients during the active-treatment period. Following the completion of the treatment period, patients were followed for an additional 28 days.

Population: Obese male and female adolescents between 12 and 16 years of age at the time of screening were enrolled from 32 centers.

Inclusion Criteria

- BMI at the time of screening that was 2 units greater than the US weighted mean for the 95th percentile based on age and gender, as outlined in the table below.

Minimum BMI for Study Eligibility		
Age	BMI	
(years)	Male	Female
12	28.5	29.5
13	29.1	30.6
14	29.8	31.3
15	30.7	31.6
16	31.8	31.9

- Age: 12 to 16 years at screening;
- Gender: male or female patients of all racial and ethnic groups. Females of childbearing potential had to have a negative serum pregnancy test at screening and randomization, and had to use an acceptable method of contraception during the study if sexually active;
- Patients without any chronic medical condition or with mild chronic medical

conditions (i.e., hypertension, asthma, arthritis, etc.) who do not require treatment or are medically stable on treatment;

- Availability of a parent or guardian to attend study visits with the patients and to be actively involved in the behavior modification plan.
- Give written informed consent before any study specific screening procedures with the understanding that the patient has the right to withdraw from the study at any time.

Exclusion Criteria: Patients meeting any of the following criteria were excluded from the study:

- BMI $\geq$ 44 kg/m^2 and/or body weight $\geq$ 130 kg
- Body weight < 55 kg
- Weight loss of $\geq$ 3 kg within three months prior to screening
- Pregnancy or lactation
- Diagnoses of diabetes requiring anti-diabetic medication
- Obesity associated with genetic disorders such as Prader-Willi, Bardet-Biedl, and Cohen syndromes
- History or presence of significant medical (e.g. renal cancer, hepatic cancer, or endocrine disorders) or psychiatric conditions or diseases which could impact on the results of the study, without prior approval of the sponsor
- Current use of dexamphetamine or methylphenidate (Ritalin) including in patients diagnosed with Attention Deficit Hyperactivity Disorder (ADHD)
- Hypothyroidism not controlled with a stable dose of thyroxine replacement therapy for at least.
- Abnormal laboratory test results of clinical significance
- Presence of chronic diarrhea or cholestasis
- Presence of active gastrointestinal disorders such as malabsorption syndrome
- Ongoing bulimia or laxative abuse
- Use of approved or experimental weight reduction medications or treatments currently or within 3 months of randomization
- Dependence on any substance of abuse, including alcoholism
- Unwilling or unable to comply with the protocol requirements or considered by the investigator to be an inappropriate candidate for the study
- A known hypersensitivity to orlistat or any of its components
- Failure to discontinue the use of all vitamin preparations one month prior to randomization
- Inability to swallow hard shell #2 capsules
- Participation in a clinical trial within 30 days of screening
- Use of any of the following prohibited medications within 3 months prior to randomization:
  - Anorexic medications, prescription and/or over the counter
  - Antidepressants, prescription and/or over the counter
  - Anticonvulsants
  - Antiarrythmic medications

- Systemic steroids other than oral contraceptives

Study Medication: Oral dosing with 120mg orlistat (marketed formulation) or placebo capsules three times per day with meals.

Efficacy Measures

Primary: The primary efficacy parameter for this study was the change in BMI from baseline to the end of the study or at study exit. Body weight was measured to the nearest one-tenth of a kilogram. Two consecutive measurements within 0.5 kg of each other were averaged and recorded. Height was measured to the nearest one-tenth of a centimeter using a wall mounted stadiometer. Two consecutive measurements within 0.5cm of each other were averaged and recorded.

Secondary: The secondary efficacy parameters included change in body weight, total cholesterol, LDL cholesterol, HDL cholesterol, LDL/HDL ratio, triglycerides, diastolic and systolic blood pressure, waist circumference, and glucose and insulin responses to an oral glucose challenge. In addition, hip circumference and categorical changes in BMI and body weight were analyzed.

Safety Measures: Discussed in detail in the Integrated Summary of Safety. Safety parameters included adverse events, laboratory tests, pulse rate, 12-lead ECG, physical examinations, linear growth, Tanner stage assessment, bone mineral content, body composition, fat soluble vitamin and beta-carotene levels, and gallbladder and renal ultrasound findings.

Study Methods: During the 2-week placebo lead-in period, patient's vital signs, weight, height, and waist and hip measurements were recorded. Patients received nutritional, behavior modification, and exercise counseling and began the recommended hypocaloric diet and exercise regimen.

Diet: Patients were maintained on a nutritionally balanced, hypocaloric diet designed to produce an initial weight loss of 0.5 to 1.0 kg/week. The caloric distribution of the diet was 30% as fat, 50% as carbohydrate, and 20% as protein, with a maximum of 300 mg/day cholesterol and 1300 mg calcium intake per day. The maximum amount of fat in the diet was not to exceed 70 g per day. Dietary caloric intake was assigned to patients according to their body weight on study day -14 (see table below). The daily caloric intake assignment was adjusted if the subject reached a BMI of 22 kg/m^2 or less or if the patient was losing weight too rapidly.

Caloric Intake Assignment		
Body Weight (Kg)	Total Calorie Intake: Male (Kcal/day)	Total Calorie Intake: Female (Kcal/day)
< 70	1400	1200
70 to < 80	1500	1300
80 to < 90	1600	1400
90 to <100	1700	1500
> 100	1800	1600

Behavior modification: All centers had behavior modification programs in place. The programs utilized unifying principles including self monitoring of diet and activity, stimulus control, behavioral substitution, speed of food intake and information and motivational support.

Exercise: Exercise guidelines were provided to help the patients establish patterns of regular physical activity and encourage the gradual development of physical conditioning.

Vital signs were recorded at each study visit. Body weight was recorded at each visit with the patient wearing street clothing and no shoes, outerwear, or accessories. Weight was measured in kilograms (kg) and recorded to the nearest one-tenth of a kg. The patient was weighed at least twice until two consecutive measurements were within 0.5 kg of each other. Height, without shoes, was measured at every visit. Height was measured in centimeter (cm) and recorded to the nearest one-tenth of a cm. The standing height was measured at least twice until two consecutive measurements were within 0.5cm of each other. Waist and hip circumference measurements were obtained monthly. Other outcome measures included: total cholesterol, LDL cholesterol, HDL cholesterol, LDL/HDL ratio, triglycerides at baseline (Day1), Weeks 13, 25, and 52 or at study exit; glucose and insulin responses to an oral glucose challenge at baseline (Day1), Week 25 and Week 52 or study end; Tanner staging at baseline (Screening), Week 25 and Week 52 or study end; serum levels of sex-hormone binding globulin, estradiol (females), and free testosterone (males) levels at baseline (Day1), Week 25 and Week 52 or study end; and electrocardiogram at baseline (Day 1) and Week 52 or study exit. A subgroup of 18 study centers performed DEXA to assess of changes in body composition at baseline and Week 52 or study exit. A total of 229 subjects had DEXA assessments (77 in the placebo group and 152 in the orlistat group).

Withdrawal criteria: Subjects could withdraw from the study at any time. Investigators could withdraw patients in the event of intercurrent illness, adverse events, treatment failure after a prescribed procedure, protocol violations, cure, administrative reasons, or other reasons. The investigator was required to report all pregnancies to the sponsor within 24 hours and all pregnancies were to be followed to their conclusion. Patients who were withdrawn from the study were not replaced.

Statistical Analyses: A total of 539 patients from 32 study centers were randomized (182 to the placebo group and 357 to the orlistat group). A total of 349 patients completed the study [117 (64%) in the placebo group and 232 (65%) in the orlistat group]. The standard deviation of change from baseline BMI is not larger than the estimated 2.6 and therefore, the power is more than 80%. Efficacy was analyzed for all patients who had baseline efficacy assessments and at least one post-baseline efficacy measurement (ITT population). Primary and secondary efficacy endpoints were also analyzed for all patients who completed a final visit at week 52 (Completers population). All efficacy endpoints were derived using the last-observation-carried-forward (LOCF) data set. Change from baseline to week 52 in BMI was analyzed using an analysis of covariance model (ANCOVA) that included change from baseline value as the response, and treatment, center, and treatment-by-center, and baseline stratification terms.

Protocol Amendments: There were no amendments to this protocol.

Results

Patient Disposition: A total of 539 patients from 32 centers were randomized. Of these 539 patients, 182 were randomized to the placebo group and 357 were randomized to the orlistat group. A similar percentage of patients in each treatment group (placebo, 64%; orlistat 65%) completed the study. The calculated compliance based on pill count was 73% in the orlistat treatment group and 72% in the placebo treatment group. Eleven subjects were excluded from the ITT analysis because they did not have a follow-up efficacy assessment

Study NM16189: Patient Disposition		
	Placebo	Orlistat
Enrolled	182	357
Included in ITT	180	348
Withdrew - Safety	3 (2)	12 (3)
Withdrew - Nonsafety	61 (34)	108 (31)
Deaths	0	0
Completed	117 (64)	232 (65)

Protocol Violations:

Five subjects (3 in the placebo group, 2 in the orlistat group) were withdrawn from the study due to protocol violations. Administration of the following medications was not permitted at the time of enrollment or during the study:

- Anorexic medications, including but not limited to fluoxetine, sertraline, paroxetine
- Antiarrhythmic medication
- Antidepressants
- Anticonvulsants
- Anxiolytics if taken regularly (i.e. benzodiazepines)
- Cyclosporine
- Dexamphetamine or methylphenidate (Ritalin)
- Fat soluble vitamins (unless given as part of the study) or fish oil supplements
- Olestra containing foods such as
- Insulin and/or oral hypoglycemic agents
- Systemic steroids other than oral contraceptives (i.e., glucocorticoids, anabolic steroids)

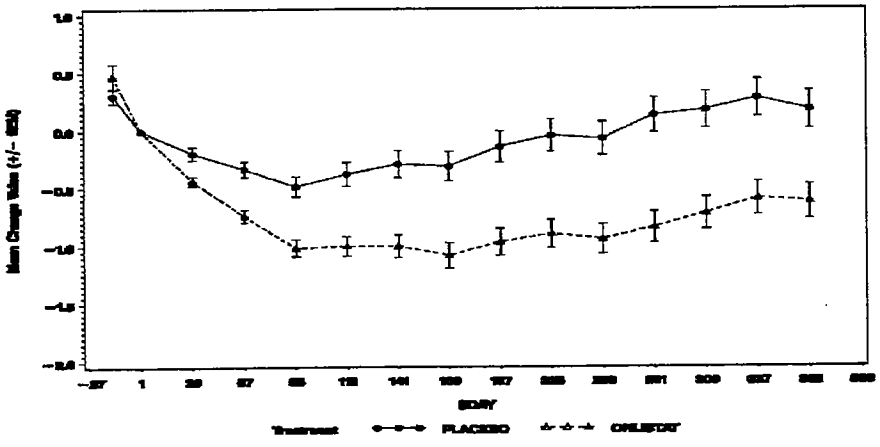
Eight subjects received incorrect study medication in the early stages of the study. Two subjects assigned to receive orlistat received placebo (one for 3 days and one for 87 days). Six subjects assigned to receive placebo received orlistat, all for less than 42 days.

Demographics: The two groups were well matched for baseline demographic characteristics (Table below). The mean age of the participants was 13.5 years, approximately 75% of the subjects were Caucasian, and the average BMI was 35.

NM16189: Patient Demographics		
	Placebo	Orlistat
N	181	352
Age (yrs.)	13.50 ± 1.24	13.61 ± 1.35
Sex		
Male	52 (28.7%)	124 (35.2%)
Female	129 (71.3%)	228 (64.8%)
Body Weight (kg)	95.11 ± 14.18	97.71 ±14.96
Body Height (cm)	163.65 ± 7.74	165.16 ± 8.43
BMI (kg/m2)	35.43 ± 4.07	35.72 ± 4.17
Race		
Caucasian	141 (77.9%)	264 (75.0%)
Black	25 (13.8%)	66 (18.8%)
Other	15 (8.3%)	22 (6.3%)
Lead-In BW loss		
< 1%	95 (52.5%)	166 (47.2%)
≥ 1%	86 (47.5%)	186 (52.8%)
Baseline BW		
< 80 kg	22 (12.2%)	36 (10.2%)
≥ 80kg	159 (87.8%)	316 (89.8%)

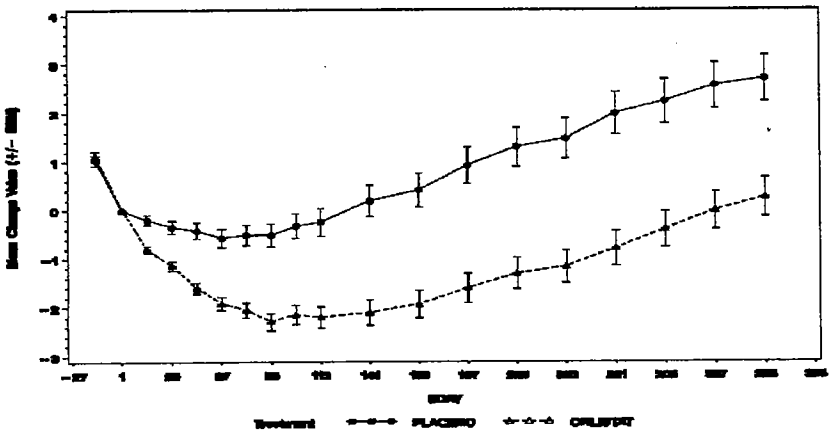
Primary Efficacy Outcomes

Body Mass Index: The primary efficacy parameter for this study was change in BMI from baseline to week 52 or study exit. During the first 12 weeks of treatment, subjects in both groups had a decrease in BMI (see figure below). In the ITT population, the least squares mean (LSM) change from baseline to study end was -0.55 kg/m^2 in the orlistat group and +0.31 kg/m^2 in the placebo-treated patients. This difference between the two treatment groups was statistically significant (p = 0.001). Similar results were seen for the Completers population. Overall, 26.5% of orlistat-treated patients and 15.7% of placebo-treated patients had at least a 5% reduction of their baseline BMI, while 13.3% of orlistat-treated patients and 4.5% of placebo-treated patients had at least a 10% reduction of their baseline BMI.



Secondary Efficacy Outcomes

Body Weight: All subjects initially lost weight during the first four weeks of the study then began to gain weight for the remainder of the study period. (see figure below) At study end, the LSM change from baseline in body weight was 0.53 kg for orlistat-treated patients and 3.14 kg for placebo-treated patients. This difference was statistically significant (p = 0.000). Similar to results seen with BMI, significantly more patients treated with orlistat had at lease 5% (19%) and a 10% (9.5%) reductions in baseline body weight than patients treated with placebo (11.7% of patients had at a least a 5% weight loss and 3.3% of patients had at lease a 10% weight loss; ($p<0.05$). .



Lipid Parameters: Very few of the patients in this study had abnormalities in serum lipids at baseline. As shown in the following table, there were no statistically or clinically significant improvements by the end of the study and no significant differences between orlistat treated subjects and placebo-treated subjects.

NM16189: Lipid Parameters					
Treatment	**N**	**Baseline**	**LSM Change**	**Difference from Placebo**	
			%	LSM	p
Total cholesterol					
Placebo	163	4.20	3.10		
Orlistat	323	4.18	2.29	-0.81	0.558
LDL cholesterol					
Placebo	163	2.50	2.99		
Orlistat	322	2.49	1.26	- 1.73	0.352
HDL cholesterol					
Placebo	163	1.08	0.65		
Orlistat	323	1.10	2.29	1.8963	0.389
Triglycerides					
Placebo	163	1.39	16.81		
Orlistat	323	1.30	22.47	5.66	0.281

Glucose and Insulin levels: The majority of patients (> 92%) in both treatment groups had normal glucose tolerance at baseline. Mean 0 minute and 120 minute glucose values were similar at baseline in the placebo and orlistat treatment groups and patients in both treatment groups had a similar decrease in these values by the end of the study. Patients in both treatment groups had a large decrease in baseline insulin levels at the end of the study. Patients treated with orlistat had a larger decrease in insulin at both the 0 minute (orlistat, -28.1; placebo -20.33) and 120 minute (orlistat, - 171.8; placebo 133.7) time points. This differences were not statistically significant however.

Anthropometric Measurements: Waist Circumference: Mean waist circumference was similar in both treatment groups at baseline (104.61 cm in the placebo group vs. 106.34 cm in the orlistat group). The LSM change from baseline to the end of the study was -2.55 cm in the orlistat treatment group and -0.62 cm in the placebo treatment group. This difference was statistically significant (p = 0.008). Hip Circumference: Mean hip circumference was similar in both treatment groups at baseline (116.03 cm in the placebo group vs. 116.57 cm in the orlistat group). The LSM change from baseline to the end of the study was -1.33 cm in the orlistat treatment group and +0.12 cm in the placebo treatment group. This difference was statistically significant (p = 0.013).

Blood Pressure: Baseline blood pressure values were similar for the two groups. The LSM change from baseline to the end of treatment for systolic blood pressure was 0.71 mmHg for orlistat-treated patients and 1.31 mmHg for placebo treated patients. This difference was not statistically significant. The LSM change from baseline to the end of treatment for diastolic blood pressure was -0.40 mmHg for the orlistat-treated patients and 1.06 mmHg for the placebo-treated patients and this difference was statistically significant (p = 0.047).

DEXA: In the one-year study , 18 sites were qualified to do DEXA measurements. The results indicate that changes in body weight are accounted for mostly by decreases in body fat and increases in fat free mass (soft tissue) (see table below).

DEXA Results for Adolescents (Study NM16189)

	Mean Change from BL		ANCOVA Results		
Parameter	Orlistat (N=152)	Placebo (N=77)	LSM Difference from Placebo	Confidence Interval	p-value
BMC (kg)	0.196	0.182	0.005	-0.051to 0.061	0.857
BMD (g/cm^2)	0.04	0.04	0.00	-0.01 to 0.01	0.666
Fat free mass soft tissue (kg)	2.116	2.312	-.0.53	-1.220 to 1.114	0.929
Fat mass (kg)	-2.401	-0.382	-1.981	-3.806 to -0.157	0.033

Note: BMC = bone mineral content; BMD = bone mineral density; BL = baseline

Subgroup and Additional Analyses: Weight management was analyzed separately in subgroups based on sex, race, age and pubertal status. These analyses were post-hoc and sample sizes were small, therefore their value is limited. Gender: The LSM change from baseline to end of treatment was –0.38 kg/m2 for female patients treated with orlistat and 0.19 kg/m2 for female patients treated with placebo and this difference was statistically significant (p = 0.048). The LSM change from baseline to the end of treatment was -1.08 kg/m2 for male patients treated with orlistat and 0.15 kg/m2 for male patients treated with placebo (p = 0.004). The gender by

treatment interaction was not significant (p = 0.1965). Race: The LSM change from baseline to study end for BMI was 0.10 kg/m2 for black patients treated with orlistat and 0.74 kg/m2 for black patients treated with placebo. For white patients the corresponding LSM change from baseline to the end of treatment for BMI was -0.72 kg/m2 for patients treated with orlistat and 0.06 kg/m2 for patients treated with placebo. The race by treatment interaction was not significant (p = 0.4089). Age: For patients aged ≤14 years, the LSM change from baseline to the end of the study for BMI was -0. 59 kg/m2 for patients treated with orlistat and 0.24 kg/m2 for patients treated with placebo (p = 0.001). For patients aged >14 years, the corresponding LSM change from baseline to the end of the study for BMI was -0.70 kg/m2 for patients treated with orlistat and -0.03 kg/m2 for patients treated with placebo (p= .211). The age by treatment interaction was not significant (p = 0.7912). Pubertal Status: For subjects who were prepubertal (Tanner stage 1 through 4) at screening, the LSM change from baseline to the end of the study for BMI was -0.76 kg/m2 for patients treated with orlistat and 0.18 kg/m2 for patients treated with placebo (p = 0.001). For Tanner stage 5 subjects, the corresponding LSM change from baseline to the end of the study for BMI was -0.65 kg/m2 for patients treated with orlistat and 1.35 kg/m2 for patients treated with placebo (p=.173). The tanner stage by treatment interaction was not significant (p = 0.4686).

Medical Officer's Conclusions: This study shows that, similar to the adult population, orlistat use in the adolescent population resulted in a small, but statistically significant change in the primary efficacy variable, BMI (-0.55 kg/m^2 in the orlistat group and +0.31 kg/m^2 in the placebo group, p=0.001). Overall, 26.5% of orlistat-treated patients and 15.7% of placebo-treated patients had a 5% reduction of their baseline BMI (p=0.005) while 13. 3% of orlistat-treated patients and 4.5% of placebo-treated patients had a 10% reduction of their baseline BMI (p=0.002). Body weight and height increased in both groups, as one would expect in this growing population. The difference in change of body weight between the groups (0.53 kg for the orlistat group vs. 3.14 kg for placebo group) was statistically significant (p = 0.001). Similar to results seen with BMI, significantly more patients treated with orlistat had 5% (19%) and a 10% (9.5%) reduction in baseline body weight than patients treated with placebo (11.7% of patients had a 5% weight loss and 3.3% of patients had a 10% weight loss; p-value for difference from orlistat-treated patients is 0.032 and 0.011, respectively). Body composition was analyzed by DEXA and showed significant decrease in fat mass (p = 0.033). Anthropometric measurements were statistically different between the orlistat and placebo groups for both waist (-2.55 cm in the orlistat group and -0.62 cm in the placebo group, p = 0.008) and hip circumference (-1.33 cm in the orlistat group and +0.12 cm in the placebo group, p = 0.013). There was no statistical difference in the effect of orlistat on blood pressure, lipid parameters, glucose or insulin levels in this low risk adolescent population.

VI.C.2. Study PP16203: This was an inpatient, single-center, double-blind, randomized, placebo-controlled, study evaluating the effect of orlistat on the mineral balance.

Objectives: The primary objective of the study was to assess the effect of orlistat on the balance (dietary intake minus urinary and fecal excretion) of selected minerals in obese subjects, 12-16 years old.

The secondary objectives of the study were:

1. To assess the effect of orlistat treatment on plasma and urine sodium and potassium and urine creatinine.
2. To evaluate the extent of fecal fat excretion induced by orlistat in this population.
3. To evaluate plasma levels of orlistat and its M1 and M3 metabolites.

Study Design: This was a single-center, double-blind, randomized, placebo-controlled, parallel-group, in-patient study in obese adolescents. Obesity was defined as a BMI of ≥ 85th percentile adjusted for age and sex at the time of screening. The study consisted of a screening period (days -21 to -1), a dosing period (days 1 to 21), and a follow-up period (day 22). Subjects were randomized to either a placebo or orlistat treatment group in a 1:1 ratio. Every attempt was made to have an equal number of male and female subjects in each treatment group. Since one of the minerals assessed, iron, could be affected by menstruation, every attempt was also made to include females of child bearing potential, who were not menstruating or expected to menstruate during the days critical for the mineral balance segment of the study (days 15 to 22 inclusive).

Population: Obese adolescent subjects between 12 and 16 years of age at the time of screening were enrolled. A total of 32 subjects (n = 32) were enrolled in the study and randomized in a 1:1 ratio to either the placebo or orlistat treatment group.

Inclusion Criteria

- BMI ≥ the 85th percentile, adjusted for age and sex (see table below).

PP16203: BMI 85th Percentile		
Age	BMI	
(years)	Male	Female
12	22.6	23.6
13	23.2	24.4
14	23.7	24.9
15	24.5	25.2
16	25.1	25.5

- Age range: 12-16 years
- Gender: male or female
- Negative serum pregnancy test at screening and randomization (females of childbearing potential only). Use of an acceptable method of contraception if sexually active
- Willingness to give written informed consent and to participate and comply with the study
- Non-smoker

Exclusion Criteria

- Treatment with prescription medications within 14 days, or over the-counter medications, including vitamin supplements, within 3 days of the study, or anticipated their need during the study with the exception of drugs which had been approved by the Sponsor including paracetamol and acetaminophen

- History of clinically relevant respiratory, cardiovascular, endocrine, hematological, gastrointestinal, renal, hepatic or neurological disorders
- History or presence of any conditions that cause malabsorption of fat (e.g., celiac disease, tropical sprue, regional enteritis, pancreatitis) or history of lactose intolerance.
- Diarrhea (> 2 liquid stools/day) during 1 week prior to the study, or constipation (ε 3 days duration) within the last 2 weeks prior to the study
- Known allergy or sensitivity to orlistat or to a component of the radio-opaque pellets including barium sulphate (minimum of 33%), calcium, zinc, or gelatin
- Donated or lost blood greater than 200 mL within 3 months prior to the start of the study
- Subjects who were on a special diet (e.g. vegetarian, kosher, lactose intolerant) or who could not fulfill the dietary requirements
- Use of, or dependence on, any substances of abuse including a history of alcohol intake;
- Unable or unwilling to comply with the protocol requirements or considered by the investigator to be unfit for the study; or
- Participated in a clinical trial within 3 months prior to entry.

Study Medication: Oral dosing with 120mg orlistat (marketed formulation) or placebo capsules three times per day with meals. Patients also received one capsule containing 10 radio-opaque markers three times a day with meals. For both treatment groups, all drugs were administered mid-meal (i.e., 5 minutes after the start of breakfast, lunch and dinner) at the study unit.

Efficacy Measures: Pharmacodynamic assessments included the balance of calcium, copper, iron, magnesium, phosphorous, and zinc. Mineral balance was defined as minerals ingested minus minerals excreted. Because variation in gut transit time could affect mineral balance, the method used to assess mineral balance needed to make no assumptions about day-to-day variations in bowel habit, was easy to perform, and practical and accurate. A method of continuous administration of radio-opaque pellets described by Cummings, et. al.[1] was used in this study to correct mineral fecal excretion by fecal recovery. Additional pharmacodynamic assessments included serum and urine levels of sodium, potassium, and urine creatinine, and fecal fat content.

Safety Measures: Safety assessments included adverse events, clinical laboratory parameters, vital signs, and 12-lead electrocardiograms (ECGs).

Study Methods: Subjects were admitted to the study center on the evening of study day –1 and were not discharged until completion of follow-up assessments on study day 22. While on the inpatient unit, subjects were maintained on a standardized meal plan of 1800kcal with 30% of calories derived from fat. The total volume of urine voided was collected in 24-hour intervals (7 am to 7 am of the following day) starting in the morning of day 10 through day 22. Fecal collection commenced on the morning of day 10 and continued through to the morning of day 22. Each sample produced was collected individually into separate labeled bags over a 24-hour period (7 am to 7 am the following day). At the end of the 24-hour period all samples collected

[1] Cummings JH, Jenkins DJA, Wiggins HS. Measurement of the mean transit time of dietary residue through the human gut. GUT 1979:17:210-218.

within that time were placed into an additional bag and given a sample number for that particular day. All samples collected were X-rayed at the study site for the number of radio-opaque markers. Samples collected on days 15 to 22 were analyzed for mineral output and for fecal fat content.

Withdrawal criteria: Subjects had the right to withdraw from the study at any time for any reason. The investigator also had the right to withdraw subjects from the study if it was in the best interest of the subject. Subjects who were discontinued prematurely from the study were not to be replaced unless the number of dropouts per treatment group was greater than 3.

Statistical Analyses: A total of 32 subjects were planned to be enrolled in two equal size groups of 16 subjects per group, with the expectation of obtaining 13 evaluable subjects per group. Assuming a standard deviation of 1.75, 80% power, ⟨= 0.05 (two-sided test), a difference of 2 mmol/24 hrs in calcium mineral balance could be detected between the two treatment groups. The standard deviation of 1.75 was observed in / ——— / an adult mineral balance study.

Protocol Amendments: There were no amendments to this protocol.

Results

Patient Disposition: Thirty-two subjects, 16 subjects in the placebo treatment group and 16 subjects in the orlistat treatment group, were enrolled in the study. Two subjects, one from each treatment group, were discontinued for refusing treatment. These subjects were not replaced. Thirty subjects completed the study.

Protocol Violations: It was necessary to redefine the analysis population used for analyses of mineral balance and fecal fat since 3 subjects did not have fecal samples (fecal marker recovery) during the day 15 to day 22 collection period. The new analysis population included subjects who completed the study and had at least one recovered fecal maker during the day 15 to day 22 collection period. Mean fecal marker recovery was 70% for the placebo treatment group and 69% for the orlistat treatment group. The population analyzed includes 14 orlistat-treated subjects and 13 placebo-treated subjects.

Demographics: The two treatment groups were balanced with respect to demographic characteristics. Mean BMI was 34.1 kg/m^2 in the placebo treatment group and 34.2 kg/m^2 in the orlistat treatment group. Overall, 44% of subjects in the placebo treatment group and 63% of subjects in the orlistat treatment group were non-Caucasian. Seven subjects in the placebo treatment group and 3 subjects in the orlistat treatment group had a BMI < 30 kg/m^2.

PP16203: Patient Demographics		
	Placebo	**Orlistat**
N	16	16
Age (yrs.)	14.0 ± 1.26	14.2 ± 1.28
Sex		
Male	6 (38%)	7 (44%)
Female	10 (63%)	9 (56%)

PP16203: Patient Demographics		
	Placebo	Orlistat
Body Weight (kg)	98.9 ± 30.62	102.0 ± 23.28
Body Height (cm)	168.9 ± 10.85	172.5 ± 9.32
BMI (kg/m^2)	34.1 ± 7.75	34.2 ± 6.37
Race		
Caucasian	9 (56%)	6 (38%)
Black	3 (19%)	4 (25%)
Other	4 (25%)	6 (38%)

Primary Efficacy Outcomes

Mineral Balance (Calcium, Copper, Iron, Magnesium, Phosphorus, and Zinc):
Mineral balances were calculated by subtracting fecal and urinary mineral content from dietary mineral intake. For all minerals, other than iron, slightly more mineral was ingested than excreted during the 24-hour period in both the placebo and orlistat treatment groups within the population with at least one fecal marker recovered. Radio opaque marker recovery was 0.69 in the orlistat group and 0.70 in the placebo group. Mean net fractional mineral absorption (percent intake) for the placebo and orlistat treatment groups are illustrated in the table below.

PP16203: Summary of Mean Mineral Balance Per 24 hours								
Mineral	Orlistat (n=14)				Placebo (n =13)			
(per 24 hrs)	Mean	SE	Median	CI	Mean	SE	Median	CI
Calcium (mmol)	2.3	1.2	2.0	-0.4, 5.1	1.9	1.5	1.4	-1.0, 4.7
Copper (µmol)	0.6	0.7	-0.4	-0.7, 2.0	0.1	0.7	0.1	-1.4, 1.5
Iron (µmol)	-64.7	20.4	-49.7	-98.0, -31.4	-40.4	10.1	-32.9	-75.0, -5.9
Magnesium (mmol)	3.0	0.2	2.7	2.5, 3.5	2.7	0.2	2.3	2.2, 3.2
Phosphorus (mmol)	6.4	1.3	6.8	3.8, 9.1	5.8	1.3	4.1	3.1, 8.6
Zinc (µmol)	7.6	8.9	10.2	-7.5, 22.7	5.0	5.3	12.8	-10.6, 20.7

Copper balance was –0.4 umol/24 hr in the orlistat group and 0.1 umol/24 hr in the placebo group. Both treatment groups had decreases in mean iron balance (-32.9 µmol/24 hour in the placebo group versus -49.7 µmol/24 hour in the orlistat group). An *ad hoc* analysis of variance for the association of menstrual cycles and iron was performed for iron balance in male *versus* female. There was no association between gender and iron balance.

Secondary Efficacy Outcomes

Electrolytes (Sodium and Potassium)
Mean serum and urine sodium and potassium levels were similar between the placebo and orlistat treatment groups at baseline. No significant differences were detected between treatment groups at Day 22 for either mean serum sodium (placebo, 141.7 mmol/L; orlistat, 142.4 mmol/L) or potassium (placebo, 4.1 mmol/L; orlistat, 4.1 mmol/L). There was also no significant difference detected in mean urine sodium (placebo, 108.2 mmol/L; orlistat, 113.4 mmol/L) or potassium (placebo, 60.0 mmol/L; orlistat, 43.0 mmol/L) levels.

Urine Volume, Creatinine Concentration, and Creatinine Excretion
No significant differences between treatment groups were seen for either mean daily urine volume (placebo, 995 ml; orlistat, 959 ml), mean urine creatinine concentration (placebo, 147 mg/dL; orlistat, 170 mg/dL) during days 15 to 22, or mean urine creatinine excretion (placebo, 1378 mg/24 hour; orlistat, 1480 mg/24 hour).

Fecal Fat
Mean fat intake was similar in both groups. Orlistat-treated subjects excreted more fat daily (mean of 15.9 g/24 hour or 27% of dietary intake) than did placebo-treated (mean of 4.1 g/24 hour or 7% of dietary intake) subjects.

Pharmacokinetic Results for Orlistat, M1, and M3: Please see Dr. Qiu's review and discussion of the pharmacokinetic results.

Sponsor's Conclusions: In obese adolescents, orlistat has low systemic exposure, significantly inhibits dietary fat absorption, has no significant effects on either mineral absorption or mineral balance, and is well tolerated. These results are consistent with those seen in orlistat-treated obese adults.

Medical Officer's Conclusions: This study has demonstrated that, with the exception of iron, there is no significant alteration in mineral balance with orlistat use, at least over a 3-week period. Copper balance was –0.4 umol/24 hr in the orlistat group and 0.1 umol/24 hr in the placebo group. Both treatment groups had decreases in mean iron balance (-32.9 µmol/24 hour in the placebo group versus -49.7 µmol/24 hour in the orlistat group). These decreases are consistent with trends seen in a previous orlistat mineral balance study conducted in male adult subjects (-10.80 ± 11.10 in the placebo treated group, -18.90 ± 10.50 in the orlistat treated group). No significant differences were detected between treatment groups at Day 22 for either mean serum sodium (placebo, 141.7 mmol/L; orlistat, 142.4 mmol/L) or potassium (placebo, 4.1 mmol/L; orlistat, 4.1 mmol/L). There was also no significant difference detected in mean urine sodium (placebo, 108.2 mmol/L; orlistat, 113.4 mmol/L) or potassium (placebo, 60.0 mmol/L; orlistat, 43.0 mmol/L) levels. Orlistat-treated subjects excreted more fat daily (mean of 15.9 g/24 hour or 27% of dietary intake) than did placebo-treated (mean of 4.1 g/24 hour or 7% of dietary intake) subjects.

VI.D. Efficacy Conclusions
Orlistat use in the adolescent population resulted in a statistically significant decrease in BMI (-0.55 kg/m^2) when compared to placebo (+0.31 kg/m^2) (p=0.001). Overall, 26.5% of orlistat-treated patients and 15.7% of placebo-treated patients had a 5% reduction of their baseline BMI (p=0.005) while 13. 3% of orlistat-treated patients and 4.5% of placebo-treated patients had a 10% reduction of their baseline BMI (p=0.002). Body weight and height increased in both groups, as one would expect in this growing population. The difference in change of body weight between the groups (0.53 kg for the orlistat group vs. 3.14 kg for placebo group) was statistically significant (p = 0.001). Similar to results seen with BMI, significantly more patients treated with orlistat had 5% (19%) and a 10% (9.5%) reduction in baseline body weight than patients treated with placebo (11.7% of patients had a 5% weight loss and 3.3% of patients had a

10% weight loss; p-value for difference from orlistat-treated patients is 0.032 and 0.011, respectively). In the adult population, approximately 60% of orlistat treated patients and 31% of placebo-treated patients had a 5% reduction of their baseline body weight while 27% of orlistat-treated patients and 11% of placebo-treated patients had a 10% reduction in body weight at one year of therapy. Body composition, analyzed by DEXA, showed significant decrease in fat mass ($p = 0.033$) with no decrease in fat free mass in adolescents evaluated. In the adult population, decreases in both fat mass and fat free mass were seen. Anthropometric measurements were statistically different between the orlistat and placebo groups for both waist (-2.55 cm in the orlistat group and -0.62 cm in the placebo group, $p = 0.008$) and hip circumference (-1.33 cm in the orlistat group and +0.12 cm in the placebo group, $p = 0.013$). There was no statistical difference in the effect of orlistat on blood pressure, lipid parameters and glucose or insulin levels in the low risk adolescent population. For most minerals, a positive balance was achieved on day 22 in both the placebo and orlistat treatment groups. Copper balance was –0.4 umol/24 hr in the orlistat group and 0.1 umol/24 hr in the placebo group. Both groups had decreases in mean iron balance (-32.9 µmol/24 hour in the placebo group versus -49.7 µmol/24 hour in the orlistat group). Negative iron balance was previously noted in mineral balance studies conducted in obese adult male subjects (-10.80 ± 11.10 in the placebo treated group, -18.90 ± 10.50 in the orlistat treated group). The etiology of the net loss of iron is unclear, though may be a consequence of the high conservation of the mineral in this age group. There was no association between gender and iron balance. No significant differences were detected between treatment groups at Day 22 for either mean serum sodium (placebo, 141.7 mmol/L; orlistat, 142.4 mmol/L) or potassium (placebo, 4.1 mmol/L; orlistat, 4.1 mmol/L). There was also no significant difference detected in mean urine sodium (placebo, 108.2 mmol/L; orlistat, 113.4 mmol/L) or potassium (placebo, 60.0 mmol/L; orlistat, 43.0 mmol/L) levels.

VII. Integrated Review of Safety

VII.A. Brief Statement of Conclusions

There were no new safety signals noted from these studies in obese adolescent subjects. Similar to the adult population, gastrointestinal adverse events including fatty/oily stools were common in the orlistat-treated group. Fat soluble vitamin levels increased during the study in all subjects, most likely because of the daily multivitamin supplementation. In the adults studies multivitamin usage was not a planned part of the protocols and the use of orlistat was associated with a lowering of plasma fat soluble vitamin levels. There is no evidence that orlistat use had an impact on pulse, height, physical exam, sexual maturation, QTc interval or sex hormone levels.

VII.B. Description of Patient Exposure

Overall, 65% of orlistat-treated patients and 63% of placebo-treated patients completed the 52 week study. The calculated compliance based on pill count was 73% in the orlistat treatment group and 72% in the placebo treatment group. The mean cumulative dose of orlistat received was 161751.5 mg of drug. Eight subjects received incorrect study medication in the early stages of the study. Two subjects assigned to receive orlistat received placebo (one for 3 days and one for 87 days). Six subjects assigned to receive placebo received orlistat, all for less than 42 days.

In the 22 day inpatient study, fourteen subjects completed the study and received a cumulative dose of 7.56 g of orlistat. One subject withdrew after 7 days of treatment (2.52 g orlistat), and another withdrew after 17 days of treatment (6.12 g orlistat).

VII.C. Methods and Specific Findings of Safety Review
Both studies were reviewed in depth for safety. The mineral balance of study PP16203 has been reviewed in the efficacy review section. Adverse events for that study are reviewed here.

VII.C.1. Study NM16189: This was a multicenter, randomized, double-blind, placebo-controlled, 54-week study conducted in obese adolescent patients.

Demographics: Six patients were excluded from the safety population because they did not have a follow-up safety assessment.

Exposure: Overall, 65% of orlistat-treated patients and 63% of placebo-treated patients completed the 52 week study (see table below). The calculated compliance based on pill count was 73% in the orlistat treatment group and 72% in the placebo treatment group. The mean cumulative dose of orlistat received was 161751.5 mg of drug.

Study NM16189: Drug Exposure		
	Placebo	Orlistat
	N = 181	N = 352
	No. (%)	No. (%)
Orlistat Group		
Treatment Duration (days)		
1 - 42	1 (<1)	18 (5)
43 - 70	-	15 (4)
71 - 98	1 (<1)	12 (3)
99 - 140	-	18 (5)
141 - 196	-	26 (7)
197 - 252	-	16 (5)
253 - 316	-	19 (5)
317 - 420	-	228 (65)
Total Cumulative Dose (MG)		
Mean	16200.0	161751.5
SD	21382.91	79961.91
SEM	15120.00	4261.98
Median	16200.0	144720.0
Min	1080	1440
Max	31320	294480
n	2	352
Placebo Group		
Treatment Duration (days)		
1 - 42	7 (4)	6 (2)
43 - 70	15 (8)	-
71 - 98	8 (4)	-
99 - 140	4 (2)	-
141 - 196	15 (8)	-
197 - 252	8 (4)	-
253 - 316	10 (6)	-
317 - 420	114 (63)	-

Of note, eight subjects received incorrect study medication in the early stages of the study. Two subjects assigned to receive orlistat received placebo (one for 3 days and one for 87 days). Six subjects assigned to receive placebo received orlistat, all for less than 42 days.

Deaths: No deaths occurred in the study population.

Serious Adverse Events: A total of 17 serious adverse events were reported in 16 subjects (6 events in the placebo group and 11 events in the orlistat group. See Appendix XI.A. for complete details. Three serious adverse events involved the gastrointestinal system: a 12-year-old male, randomized to orlistat, was hospitalized on day 19 with appendicitis; a 15-year-old female, randomized to orlistat, was hospitalized on day 168 for cholelithiasis and underwent cholecystectomy; and a 14-year-old female, randomized to orlistat, experienced right upper quadrant pain initially on day 67, was hospitalized on day 321 for laparoscopic cholecystectomy.

Adverse Events Leading to Withdrawal: The percentage of subjects who withdrew from the study because of adverse events was similar in both treatment groups (2% in the placebo group and 3% in the orlistat group). The most common types of events leading to treatment discontinuation were gastrointestinal disorders, especially in the orlistat treatment group. Two of the adverse events leading to discontinuation were serious and discussed above (a demyelinating disorder in a patient from the placebo group and depression in a patient from the orlistat group).

Adverse Events: Overall, 94% of placebo-treated and 97% of orlistat-treated patients reported at least one adverse event during the study (see table below). Gastrointestinal disorders were the most frequently reported adverse events, occurring in 71% of the placebo-treated patients and 88% of the orlistat-treated patients. A slightly higher percentage of patients treated with orlistat reported upper respiratory infections (32% versus 27%) and headache (38% versus 31%) than patients treated with placebo.

NM16189: Adverse Events, by Body System		
	Placebo	Orlistat
Subjects Receiving Dose	181	352
Subjects with At Least 1 AE	170 (94%)	342 (97%)
Events:		
Gastrointestinal	139	311
Hepato-biliary	2	6
Cardiovascular	2	2
Body as a whole	28	50
Musculoskeletal	51	94
Nervous	70	161
Infections	124	257
Respiratory	70	113
Skin and Appendages	31	70
Special Senses	25	27
Reproductive and Breast	22	33
Injury and Poisoning	49	106
Psychiatric	8	18
Immune	3	15
Blood and Lymphatic	3	3
Surgical/Medical Procedure	5	8

NM16189: Adverse Events, by Body System, continued		
	Placebo	Orlistat
Endocrine/Metabolic	4	15
Urogenital	2	8
Vascular	2	2
Benign Neoplasm	1	2

Gastrointestinal Adverse Events: Based on orlistat's mechanism of action, the frequency of gastrointestinal adverse events were much higher in the active-treatment group, as expected (see table below).

NM16189: Gastrointestinal Adverse Events		
	Placebo	Orlistat
	(N=181)	(N=352)
Fatty / Oily Stool	15 (8.3)	177 (50.3)
Oily Spotting	7 (3.9)	102 (29.0)
Oily Evacuation	3 (1.7)	82 (23.3)
Flatus with Discharge	5 (2.8)	70 (19.9)
Flatulence	8 (4.4)	32 (9.1)
Fecal Incontinence	1 (0.6)	31 (8.8)

Renal and Gallbladder Ultrasound:
Renal Ultrasound: Ten placebo subjects had abnormal renal ultrasounds at baseline including one patient with a renal calculus. Two orlistat patients had abnormal renal ultrasounds at baseline including one patient with a renal calculus. At the end of treatment, there were no new findings in the placebo group. In the orlistat group, one patient was found to have mild left hydronephrosis and one patient had a 6 mm echogenic focus seen. Repeat ultrasound did not show any evidence of a renal calculus. Gall Bladder Ultrasound: Of the 343 orlistat patients who had a baseline gall bladder ultrasound, 14 had a baseline abnormality including 3 patients with gallstones and 8 patients with fatty liver infiltration or hepatomegaly. At the end of the study, six (2%) orlistat patients were found to have asymptomatic cholelithiases. All were female and experienced weight loss ranging from 3.6 kg to 32.9 kg during the study. A seventh patient was found to have multiple gall bladder calculi on ultrasound after complaining of flank pain at day 167 after a 15.8 kg weight loss. The patient had a subsequent cholecystectomy. Of the 177 placebo patients who had a baseline gall bladder ultrasound, 8 had a baseline abnormality including 2 patients with gallstones; one patient was post cholecystectomy and 4 patients with fatty liver. One (0.05%) placebo patient was found to have gallstones on ultrasound at the end of the study. These findings are similar to what has been observed in the adult population. Risk factors for gallstone formation include female gender, obesity and rapid weight loss. Therefore, the incidence in gallstone formation was not unexpected.

Laboratory: No significant changes from baseline were seen in either treatment group for any laboratory parameter. The percentage of patients with a marked laboratory abnormality was similar between treatment groups. The most common marked laboratory abnormality was hematuria and high red blood cells in urine (54 subjects in the orlistat group (17%) and 26 subjects (16%) in the placebo group). All but one of the subjects was female and abnormalities were associated with menses and normalized on repeat testing. Elevated TSH levels were

detected in 6 subjects in the orlistat group and no subjects in the placebo group during the study. None of the patients were receiving thyroid hormone replacement at the start of the study. Three of the patients had elevated TSH levels at baseline and three of the patients had a single, non-replicated elevated TSH. Eleven patients receiving orlistat had elevated liver transaminase levels during the study. Most of these were single events and were normal on repeat testing. Two subjects had abnormal liver function tests at baseline and levels that were intermittently elevated during the study. Fifteen patients receiving orlistat and in five patients receiving placebo had elevated potassium levels. The majority returned to the normal range upon repeat testing. Seven patients receiving orlistat had elevated sodium levels. Most of these were single occurrences and normalized on repeat testing. One patient in the placebo treated group had a low ionized calcium level that normalized on repeat testing. Four subjects in the orlistat group and two subjects in the placebo group had elevated parathyroid PTH hormone levels during the study. Thirty-one patients receiving orlistat and twenty-three patients receiving placebo had markedly elevated prothrombin times. Abnormalities in prothrombin time could be an indication of Vitamin K deficiency. However, these abnormalities spanned both orlistat and placebo treated groups and were found to cluster at one or two investigative sites. Thus, the abnormalities were felt to be related to improper specimen handling and storage. The majority returned to normal upon repeat testing.

Laboratories of Special Interest

Sex steroids: Levels of free testosterone and sex hormone binding globulin were not significantly different from baseline to the end of the study among girls in the study population. There was no difference between treatment groups either. There was a decrease in estradiol levels among girls in both treatment groups. This decrease was greater for girls in the orlistat group than girls in the placebo group. The LSM change from baseline to the end of the study for estradiol was -7.5 pg/mL for the orlistat group and 0.7 pg/mL for the placebo group ($P = 0.045$). This most likely represents decreased peripheral conversion of androgen to estrogen due to the reduced fat mass. Levels of estradiol and sex hormone binding globulin decreased slightly during treatment among boys in both groups. Levels of free testosterone increased slightly in both groups. The changes were similar between treatment groups.

Fat Soluble Vitamins: All subjects in the trial were maintained on a multivitamin preparation during the course of the trial. In general, the levels of vitamins A, D, E, and beta-carotene increased during treatment for patients in both treatment groups (see table below). At baseline, 16 subjects in the placebo group and 27 subjects in the orlistat group had low Vitamin D levels while 2 subjects in the placebo group and 17 subjects in the orlistat group had low Vitamin A levels. Levels of vitamins D and A increased slightly in both the placebo and orlistat treatment groups and there was no significant difference between the two groups. Five subjects had low Vitamin D levels at study end (2 in the orlistat group and three in the placebo group). All had baseline values of Vitamin D that were low (see second table below). One subject in the orlistat group had a low Vitamin A level at study end. At baseline, one subject in the placebo group and one subject in the orlistat group had low Vitamin E levels. The levels of vitamin E increased to a greater extent in the placebo group when compared to the orlistat group, but the difference was not statistically significant. No subjects had low Vitamin E levels at study end. At baseline, 18 subjects in the placebo group and 43 subjects in the orlistat group had low beta-carotene levels.

The increase in beta-carotene levels for patients in the placebo group was significantly greater than the increases for patients in the orlistat group. The clinical significance of low antioxidant levels, such as beta-carotene, remains unclear.

NM16189: Summary of Vitamin Levels – Baseline and Study Completion, ANCOVA Results

					Difference from Placebo			
Parameter (normal values)	Grp	N	Baseline Mean	LSM Change from BL	LSM	SE	Confidence Interval	p-value
Vitamin A	Pl	150	48.53	1.82				
(30-90 µg/dl)	Orl	307	49.53	3.33	1.51	1.00	-0.47 to 3.48	0.134
Beta Carotene	Pl	150	8.81	3.00				
(3-85 µg/dl)	Orl	307	7.84	0.59	- 2.40	0.64	- 3.66 to – 1.15	0.000
25OH Vitamin D	Pl	150	18.07	1.79				
(22.4-116.6 nmol/L)	Orl	313	17.69	1.40	- 0.39	0.69	-1.74 to 0.96	.571
Vitamin E	Pl	150	810.01	52.18				
(696 – 3369 µmol/L)	Orl	307	797.38	11.92	- 40.26	23.65	-86.75 to 6.23	0.089
Pl- placebo group; Orl – Orlistat group								

NM16189: Low Baseline Vitamin Values

		Placebo N = 150 (%)	Orlistat N = 307[a] (%)
Vitamin A (normal range = 30 - 90 ug/dL)			
Baseline value - low		2 (1.3)	7 (2.3)
Low follow-up value[b]			
Two or more consecutive[c]			1 (14.3)
Last Value	Low		1
25 Hydroxy Vitamin D (normal range = 8.9 - 46.7 ng/mL)			
Baseline value - low		16 (10.7)	27 (8.6)
Low follow-up value[b]			
Two or more consecutive[c]		6 (37.5)	9 (33.3)
Last Value	Low	2	3
	Normal	2	5
	Missing	2	1
Vitamin E (normal range = 300 - 1580 ug/dL)			
Baseline value - low		1 (0.7)	1 (0.3)
Beta Carotene (normal range = 3 - 85 ug/dL)			
Baseline value - low		18 (12.0)	43 (14.0)
Low follow-up value[b]			
Two or more consecutive[c]		2 (11.1)	10 (23.3)
Last Value	Low	2	2
	Normal		7
	Missing		1

[a] There were 313 evaluable patients for the measurement of vitamin D.
[b] % calculated based on number of patients with normal baseline values Possibly including baseline.
[c] Based on study specific required vitamin supplementation.

Other Safety Tests

Physical Examination: There were no clinically meaningful differences in physical examination findings between groups. Tanner Stage: Patients in both the orlistat treatment group and the placebo treatment group experienced normal sexual maturation during the study and there were no notable differences between treatment groups. Height: Patients in both treatment groups grew during the study and were taller at the end of treatment than at baseline. The change in height from baseline to the end of the study was similar in both treatment groups (1.91 cm in the placebo group versus 1.82 cm in the orlistat group). ECG and Pulse: There were no significant changes from baseline in pulse or QTc interval in either the treatment or placebo group. Twenty-three patients (9 in the placebo group and 14 in the orlistat group) had an abnormal ECG at baseline including left axis deviation; left ventricular hypertrophy; intraventricular conduction defects; right bundle branch block; 1st degree AV block; sinus bradycardia; sinus tachycardia; ST-T wave changes; and Wolff Parkinson White (WPW) syndrome. At the end of treatment few patients had new abnormalities, which were either not considered as being clinically significant or were related to underlying conditions.

Medical Officer Conclusions: There are no new safety signals noted from this study in obese adolescent subjects. Gastrointestinal adverse events were common in the orlistat treated group (50.3% with fatty/oily stools). There were also two serious adverse events of gallbladder disease that required surgical intervention. These findings are similar to what has been observed in the adult population. There is no evidence that orlistat use had an impact on growth, sex hormone levels or sexual maturation. There were no significant changes from baseline in pulse or QTc interval in either the treatment or placebo group. Fat soluble vitamin levels increased during the study in all subjects due to the daily multivitamin supplement. Vitamin levels were lower in the orlistat treated group compared to placebo. These differences were statistically significant for beta Carotene (3.00 µg/dl in the placebo group and 0.59 µg/dl in the orlistat group, $p = 0.001$) and Vitamin E (52.18 µmol/L in the placebo group and 11.92 µmol/Lin the orlistat group, $p = 0.089$). These results are similar to what was observed in the adult population.

VII.C.2. Study PP16203: This is an inpatient, single-center, double-blind, randomized, placebo-controlled, parallel-group, in-patient study in obese adolescents evaluating the effect of orlistat on the balance of selected minerals.

Demographics: Sixteen subjects were enrolled in the study; all are included in the safety population.

Exposure: Fourteen subjects completed the study and received a cumulative dose of 7.56 g of orlistat. One subject withdrew after 7 days of treatment (2.52 g orlistat), and another withdrew after 17 days of treatment (6.12 g orlistat).

Deaths: No deaths occurred in the study population.

Serious Adverse Events: No serious adverse events were reported during this study.

Adverse Events Leading to Withdrawal: No withdrawals attributed to adverse events were reported during this study.

Adverse Events: Adverse events were reported by 15 orlistat-treated subjects and 13 placebo-treated subjects. Consistent with other studies, the incidence of GI adverse events, specifically fatty/oily stool, was higher in the orlistat treated group (orlistat, 44%; placebo, no subjects).

PP16203: Adverse Events, by Body System		
	Orlistat	Placebo
Subjects Receiving Dose	16	16
Subjects with At Least 1 AE	15 (94%)	13 (81%)
Events:		
Gastrointestinal	13 (81)	9 (56)
Musculoskeletal	6 (38)	6 (38)
Injury and Poisoning	5 (31)	2 (13)
Body as a whole	2 (13)	5 (31)
Endocrine/Metabolic	4 (25)	3 (19)
Nervous	3 (19)	5 (31)
Infections	3 (19)	5 (31)

Laboratory: Three marked laboratory abnormalities were reported in 3 different female patients. A 15-year old Caucasian female in the placebo treatment group, had glycosuria on day 22. Microscopic evaluation showed the presence of white blood cells and epithelial cells. The laboratory assessment was not repeated. A 14-year-old Caucasian female in the orlistat treatment group, had hematuria on day 22 (+4) which returned to normal (0) on day 32. A 13-year-old Black female in the orlistat treatment group had an ALT of 23 U/L at baseline that increased to 79 U/L on day 22. This was the last value reported and not followed up. AST and GGT levels also increased from 15 U/L at baseline to 33 U/L on day 22 and 52 U/L at baseline to 76 U/L on day 22, respectively.

Other Safety Tests
No clinically significant changes in vital signs, physical examinations, or ECGs were noted during this study. No pregnancies were reported during the study.

Medical Officer Conclusions: There were no unexpected safety signals seen in this small, short-term trial. The most common adverse events were gastrointestinal (81% in the orlistat group vs. 56% in the placebo group).

VII.D. Adequacy of Safety Testing
The safety testing conducted in these two trials was adequate to evaluate known safety concerns and to detect new safety signals if they exist.

VII.E. Summary of Critical Safety Findings and Limitations of Data
There were no new safety signals noted from these studies in obese adolescent subjects. Gastrointestinal adverse events were common with the orlistat treated group (50.3% with fatty/oily stools). There were also two serious adverse events of gallbladder disease (one cholelithiasis and one cholecystitis) that were required surgical intervention. Ultrasound studies

showed 6 subjects in the orlistat group and 2 subjects in the placebo group developed gallbladder abnormalities during the year of the study. These findings are similar to what has been observed in the adult population and is a known potential complication of weight loss. Fat soluble vitamin levels increased during the study in all subjects due to the daily multivitamin supplement. Vitamin levels were lower in the orlistat treated group compared to placebo. These differences were statistically significant for beta Carotene (3.00 µg/dl in the placebo group and 0.59 µg/dl in the orlistat group, p = 0.001) and Vitamin E (52.18 µmol/L in the placebo group and 11.92 µmol/Lin the orlistat group, p = 0.089). These results re similar to those observed in the adult population. There were no significant changes from baseline in pulse or QTc interval in either the treatment or placebo group. There is no evidence that orlistat use had an impact on growth, sex hormone levels or sexual maturation.

VIII. Dosing, Regimen, and Administration Issues

A single dose of orlistat was utilized in these clinical trials in obese adolescents. The dose used in these studies was the current marketed adult dose, 120mg t.i.d. The majority (88%) of subjects enrolled in these studies had a baseline body weight over 80kg which is comparable to a normal weight adult population.

IX. Use in Special Populations

IX.A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

These studies of orlistat use in the obese adolescent population enrolled both male and females subjects. Results were adequately analyzed for the effect of gender and none was found.

IX.B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The efficacy and safety of orlistat use in the adolescent population correlates with that seen with orlistat use in the adult population. Although these adolescent studies enrolled subjects representing multiple races and spanned the adolescent ages from 12 – 16 years, the sample size for races other than white are probably too small to make definitive statements about efficacy or safety and the age range is too narrow to dissect by age.

IX.C. Evaluation of Pediatric Program

The pediatric program and the results submitted in this application has addressed all critical issues noted in the Pediatric Written Request.

IX.D. Comments on Data Available or Needed in Other Populations

Orlistat use in the geriatric population should be analyzed.

X. Conclusions and Recommendations

X.A. Conclusions

The currently marketed dose of orlistat that has been shown to be safe and effective for weight management in the adult population is also safe and effective for use in weight management in

the adolescent population, ages 12 to 16 years. The observed weight loss effect is not as robust as what was seen in the adult population, but remains statistically and perhaps clinically significant.

X.B. Recommendations

Approve

XI. Appendix

XI.A. Study NM16189: Serious Adverse Events

1) A 17 year-old female, randomized to placebo, was hospitalized on day 280 with acute demyelinating encephalomyelitis. She had received the meningococcal vaccine on study day 97 as part of a regional vaccination program. The last dose of study medication was approximately study day 275.

2) A 16-year-old female, randomized to placebo, was seen in the emergency room on day 77 with Bell's palsy.

3) A 15-year-old female, randomized to placebo, was hospitalized on day 213 with pneumonia. Study medication was interrupted from study day 212 to study day 215.

4) A 13-year-old female, randomized to placebo, was hospitalized on study day 33 with asthma exacerbation. She had a history of reactive airway disease and sinusitis. Symptoms resolved and she was discharged on study day 41, and she resumed study drug on day 43. She was readmitted with another acute on study day 251 which also resolved after 4 days of treatment.

5) A 14-year-old female, randomized to placebo, was hospitalized on day 361 with intermittent right side pain. Study drug administration was not interrupted.

6) A 14-year-old female, randomized to orlistat, was hospitalized on day 364 for excision and drainage of a pilonidal cyst.

7) A 14-year-old female, randomized to orlistat, was hospitalized on day 74 for suicidal ideation.
8) A 14-year-old female, randomized to orlistat, was hospitalized on day 83 for an asthma exacerbation. The symptoms resolved and the patient was discharged on day 86.

9) A 12-year-old male, randomized to orlistat, was hospitalized on day 93 with seizures. The patient had a history of arachnoid brain surgery and nighttime seizures. The study medication was held on study day 92 and resumed on study day 98.

10) A 15-year-old male, randomized to orlistat, was hospitalized on day 178 for deviated septum after a traumatic incident.

11) A 12-year-old male, randomized to orlistat, was hospitalized on day 19 with appendicitis. Study medication was held from study day 19 to study day 22.

12) A 15-year-old female, randomized to orlistat, was hospitalized on day 168 for cholelithiasis and underwent cholecystectomy.

13) A 14-year-old female, randomized to orlistat, experienced right upper quadrant pain initially on day 67. She underwent evaluation and was hospitalized on day 321 for laparoscopic cholecystectomy.

14) A 16-year-old male, randomized to orlistat, was hospitalized on day 108 for adenoidectomy. Study medication was interrupted between study day 108 and study day 111.

15) A 13-year-old female, randomized to orlistat, was hospitalized on day 334 for aseptic meningitis. Study medication was interrupted between study day 333 and study day 337.

16) A 15-year-old male, randomized to orlistat, was hospitalized on day 247 for depression.

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

/s/

Theresa Kehoe
12/12/03 12:51:13 PM
MEDICAL OFFICER

Eric Colman
12/12/03 12:55:48 PM
MEDICAL OFFICER

MEDICAL TEAM LEADER MEMORANDUM

DECEMBER 10, 2003

NDA: 20-766

DRUG: Orlistat

COMPANY: Roche

SUBJECT: sNDA for Pediatric Exclusivity

PRIMARY REVIEWER: Theresa Kehoe, M.D.

DATE SUBMITTED: 23 June 2003

I. BACKGROUND

Orlistat, a pancreatic lipase inhibitor, was approved for the treatment of obesity in adults on April 23, 1999. The drug is to be taken three times a day with meals. On August 9, 2000, the Agency issued a Written Request for studies of orlistat in pediatric patients. Two studies were requested: 1) A 52-week randomized, double-blind, placebo-controlled study in obese adolescents aged 12 to 16 years; and 2) A 3-week, randomized, double-blind, placebo-controlled mineral balance study in obese adolescents.

Following a meeting with the Pediatric Exclusivity Board, it was determined that Roche conducted the two studies in accordance with the August 9, 2000 Written Request. Based on the results of the two pediatric studies, Roche is proposing to amend the product labeling.

II. Synopsis of Clinical Study NM16189

This was a randomized, double-blind, placebo-controlled 52-week study of 539 obese adolescents, aged 12 to 16 years. All subjects had a baseline body mass index (BMI) that was at least 2 units greater than the U.S. weighted mean for the 95th percentile based on age and gender. To take into account the fact that adolescents are growing, the change in BMI rather than the change in body weight, was used as the primary efficacy endpoint.

Patients were maintained on a nutritionally balanced, hypocaloric diet designed to produce an initial weight loss of 0.5 to 1.0 kg/week. The caloric distribution of the diet was 30% as fat (optimally as 10% saturated, 10% monounsaturated, and 10% polyunsaturated), 50% as carbohydrate, and 20% as protein, with a maximum of 300 mg/day cholesterol and 1300 mg calcium intake per day. The maximum amount of fat in the diet was not to exceed 70 g per day. To reduce the risk for developing fat-soluble vitamin deficiencies, all participants were instructed to take a daily multivitamin at least 2 hours before or after intake of orlistat.

The principal safety assessments included physical examinations, linear growth, routine chemistry and hematology parameters, fat-soluble vitamin levels, bone mineral density and content, body composition, and renal and hepatic ultrasounds (to evaluate for stones).

A total of 539 subjects were randomized in a 2:1 fashion to either placebo or orlistat TID with meals. The two groups were well-matched for baseline demographic characteristics. The mean age was 13.5 years, approximately 68% of the subjects were female, 76% were Caucasian, and the average BMI was 35 kg/m^2. Approximately 64% of the patients in each treatment group completed the one-year study.

In a LOCF analysis, the orlistat-treated group had a decrease in the mean BMI of 0.55 kg/m^2, while the placebo-treated subjects had an increase in the mean BMI of 0.31 kg/m^2 ($p=0.001$). In a responder analysis, 27% of the orlistat-treated patients and 16% of placebo-treated subjects had a decrease of at least 5% in baseline BMI (nominal p=xx). The orlistat group had a mean increase in body weight of 0.5 kg; whereas the placebo group had a mean increase in weight of 3.1 kg (nominal $p<0.001$). There was no evidence that the efficacy of the drug was significantly different in males vs. females. In a subgroup of subjects who had DEXA assessment of body composition, orlistat-induced weight loss was due primarily to a reduction in body fat. There was no evidence that fat-free mass declined following weight loss.

There were very small changes, generally favoring orlistat treatment, in the blood pressure, lipoprotein lipid, and serum glucose and insulin levels.

No patient died during or within 30 days following the trial. Three percent of patients in each treatment group reported at least one serious adverse event. Two patients from the orlistat group had serious events related to the gall bladder; one was cholelithiasis and the other was gall bladder disorder. Both subjects had a cholecystectomy. Three percent of the subjects in the orlistat group and 2% of the placebo subjects withdrew prematurely due to an adverse event. The majority of the events leading to withdrawal in the orlistat group were gastrointestinal.

Regarding treatment-emergent adverse events, as expected, gastrointestinal adverse events were much more common in orlistat- vs. placebo-treated subjects. Fatty/oily stool, oily spotting, and oily evacuation were reported by 50% to 23% of orlistat subjects and 8% to 2% of placebo patients.

There were no clinically meaningful differences between groups in the changes from baseline to endpoint in the laboratory parameters assessed in this study.

The mean serum levels of vitamins A, D, E, and beta carotene all increased from baseline to Week 52 in both treatment groups. The difference of -2.4 ug/dl in level of beta carotene between groups was statistically significant and the difference of -40.2 ug/dl in the level of vitamin E between placebo and orlistat groups was of borderline statistical significance. Fourteen percent of orlistat-treated patients and none of the placebo patients had a low vitamin A level on at least two or more consecutives measurments, and 23% of orlistat and 11% of placebo subjects had a low level of beta carotene on at least two or more consecutive measurements.

Ten placebo patients had abnormal renal ultrasounds at baseline including one patient with a renal calculus while two orlistat patients had abnormal renal ultrasounds at baseline including one patient with a renal calculus. At the end of treatment, there were no new findings in the placebo group. In the orlistat group, one patient was found to have mild left hydronephrosis and one patient had a 6 mm echogenic focus seen. A repeat renal ultrasound on that patient did not show any evidence of a renal calculus.

No patients had acute cholelithiasis during the study. Of the 343 orlistat patients who had a baseline gall bladder ultrasound, 14 had a baseline abnormality including 3 patients with gall stones and 8 patients with fatty liver infiltration or hepatomegaly. Of the 177 placebo patients who had a baseline gall bladder ultrasound, 8 had a baseline abnormality including 2 patients with gall stones, one patient was post cholecystectomy and 4 patients with fatty liver. At the end of the study, six orlistat patients were found to have asymptomatic cholelithiases. Five of those six patients lost large amounts of weight ranging from 8.2 kg to 29.4 kg and two of those patients were sisters. A seventh patient was found to have multiple gall bladder calculi on ultrasound after complaining of flank pain at day 167 after a 15.8 kg weight loss. The patient had a subsequent cholecystectomy. One placebo patient was found to have gall stones on ultrasound at the end of the study.

III. Synopsis of Mineral Balance Study

This was a 3-week, randomized, double-blind, placebo-controlled, study of 32 obese adolescents. Sixteen subjects were randomized to each treatment group. Fourteen orlistat and 13 placebo subjects provided mineral balance data. The primary objective was to assess, in orlistat vs. placebo-treated subjects, the balance of the following minerals: calcium, copper, iron, magnesium, phosphorus, and zinc. Mineral balance was determined during a 24-hour period after 21 days of drug or placebo treatment.

As shown in the following table, aside from iron balance, which was negative for both treatment groups, a positive 24-hour balance was noted for all minerals.

Table 1. Summary of Mean Mineral Balance Per 24 hours

Mineral (per 24 hrs)	Orlistat (n=14)				Placebo (n=13)			
	Mean	SE	Median	CI	Mean	SE	Median	CI
Calcium (mmol)	2.3	1.2	2.0	-0.4, 5.1	1.9	1.5	1.4	-1.0, 4.7
Copper (µmole)	0.6	0.7	-0.4	-0.7, 2.0	0.1	0.7	0.1	-1.4, 1.5
Iron (µmole)	-64.7	20.4	-49.7	-98.0, -31.4	-40.4	10.1	-32.9	-75.0, -5.9
Magnesium (mmol)	3.0	0.2	2.7	2.5, 3.5	2.7	0.2	2.3	2.2, 3.2
Phosphorus (mmol)	6.4	1.3	6.8	3.8, 9.1	5.8	1.3	4.1	3.1, 8.6
Zinc (µmole)	7.6	8.9	10.2	-7.5, 22.7	5.0	5.3	12.8	-10.6, 20.7

IV. COMMENTS

Roche has conducted, in accordance with the Written Request, two studies in adolescent subjects with obesity. The data provide reasonable evidence that, similar to obese adults, the drug is of modest benefit in the treatment of adolescents with obesity. No safety issues specific to the pediatric population were identified in these studies.

V. RECOMMENDATION

As of Thursday December 11, 2003, Roche had verbally agreed to all of the Division's suggested labeling changes.

I agree with Dr. Kehoe's recommendation that this sNDA be approved.

/S/

Eric Colman, MD

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

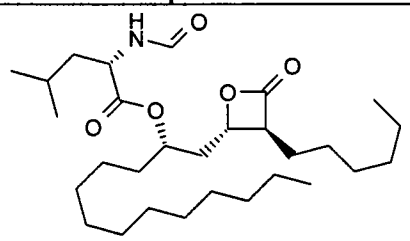
20-766/S-018

Chemistry Review(s)

CHEMIST'S REVIEW	1.ORGANIZATION DMEDP, HFD-510	2. NDA NUMBER 20-766
3. NAME AND ADDRESS OF APPLICANT		4. SUPPLEMENT NUMBER,DATE
Hoffmann-La Roche Inc 340 Kingsland Street Nutley, NJ 07110-1199 (973) 562-5550		SE5-018, 6/23/03 UF date 12/24/03
5. NAME OF THE DRUG Xenical	6. NONPROPRIETARY NAME Orlistat	8. AMENDMENT,DATE
7. SUPPLEMENT PROVIDES FOR: A request for a pediatric exclusivity determination.		N/A
9. PHARMACOLOGICAL CATEGORY Anti-obesity	10. HOW DISPENSED Rx	11. RELATED IND/NDA/DMF
12. DOSAGE FORM Capsule	13. POTENCY 120 mg	NA

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

This clinical efficacy supplement provides for a request for a pediatric exclusivity determination. Hoffmann-La Roche Inc. claims a categorical exclusion from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(b). The proposed action will increase the use of the active moiety but the estimated concentration of the substance at the point of entry into the environment will be well below 1 part per billion. No extraordinary circumstances exist that would significantly affect the quality of the environment.

16. CONCLUSION AND RECOMMENDATION

From a chemistry viewpoint, satisfactory information has been provided to grant an EA categorical exclusion.

17. REVIEWER NAME	18. REVIEWER SIGNATURE	19. DATE COMPLETED
Martin Haber, Ph.D.		October 28, 2003

DISTRIBUTION: ORIGINAL JACKET K. Johnson O. Elekwachi M. Haber

R/D Init by: Dr. Mamta Gautam-Basak, Chemistry Team Leader

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

/s/

Martin Haber
10/28/03 11:05:37 AM
CHEMIST

EA

Mamta Gautam-Basak
10/28/03 11:42:28 AM
CHEMIST
Concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-766/S-018

Statistical Review(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	20766/SE5-018
Name of drug:	Xenical® (orlistat) capsules
Applicant:	Hoffmann-La Roche, Inc.
Indication:	Weight management of obese pediatric patients
Documents reviewed:	Location of the sNDA in EDR (electronic documents room): \\CDSESUB1\N20766\S_018 and amendments dated 7-31-03, 8-19-03, and 8-26-03.
Project manager:	Oluchi Elekwachi, Pharm.D. (HFD-510)
Clinical reviewer:	Theresa Kehoe, M.D. (HFD-510)
Dates:	Submitted 6/23/03
Statistical reviewer:	Japobrata Choudhury, Ph.D. (HFD-715)
Statistics team leader:	Todd Sahlroot, Ph.D. (HFD-715)

Keywords: NDA review, clinical studies, pediatric exclusivity

Contents:

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

Study NM16189 has provided statistical evidence in favor of orlistat with respect to the primary efficacy variable change from baseline to the end of the study for BMI.

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

The applicant has submitted this Prior-Approval (i.e., already approved for adults) Efficacy Supplement for pediatric exclusivity. In support of this, it has provided results from the following clinical trial:

Protocol No.	Location of Synopsis (Module 2) Location of Report (Module 5)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.5 Efficacy and Safety Studies								
NM16189		1. Efficacy and safety 2. Changes in obesity related risk factors	Multicenter, randomized, double-blind, placebo-controlled, parallel study	120 mg capsules oral tid	539	Obese adolescent patients	52 weeks of treatment	Complete Full

Note: tid = three times daily.

1.3 PRINCIPAL FINDINGS

Study NM16189 has provided statistical evidence in favor of orlistat with respect to the primary efficacy variable change from baseline to the end of the study for BMI.

Some discussion on subgroup results is at the end of the Section 2.3.3.1.5 Efficacy Results (Sponsor's Analyses).

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

Specific Indication: 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^2 or $\geq$27 kg/m^2 in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia).

Note: New Drug Application is abbreviated by NDA. Except where specifically mentioned otherwise (as notes, reviewer's comments, conclusions, etc.), all other results and statements in this document are the sponsor's. The reviewer's silence does not imply his agreement with the sponsor's statements. Whatever the reviewer has verified and believes to be true is specifically stated so. In particular, the material in Sections 2.1 to 2.3.2 (indented) is almost verbatim from the sponsor's submission. Elsewhere, sponsor's statements may be slightly changed for brevity or for clarity.

Parts of the synopsis provided by the sponsor follow.

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT - A double-blind, placebo- controlled, 54- week study of the efficacy and safety of Xenical (orlistat) in the weight management of obese pediatric patients. Research report 1011426/ June 6, 2003.

INVESTIGATORS / CENTERS AND COUNTRIES - This was a multicenter trial in the US and Canada. A complete list of investigators is provided in the Study Documentation section of this report.

PERIOD OF TRIAL - August 8, 2000 to September 12, 2002

CLINICAL PHASE - IV

OBJECTIVES - The primary objectives of this study were to characterize the efficacy of orlistat as an adjunct to diet in the treatment of obese pediatric patients and to characterize the safety profile of orlistat in obese pediatric patients, using the following endpoints: gastrointestinal tolerability; linear growth and Tanner pubertal stage assessment; bone mineral content and body composition; fat-soluble vitamins, beta-carotene, PTH, and serum calcium levels; gall bladder and renal ultrasound.

The secondary objective of this study was to characterize changes in obesity related risk factors including total cholesterol, LDL cholesterol, HDL cholesterol, LDL/ HDL ratio, blood pressure, triglycerides, waist circumference, and glucose and insulin responses to an oral glucose challenge.

STUDY DESIGN - This was a multicenter, randomized, double-blind, placebo-controlled, parallel study of obese adolescents. Following a 2-week placebo lead-in period, patients were randomized to receive either orlistat or placebo in a 2: 1 ratio as an adjunct to a hypocaloric diet for 52 weeks. All patients received nutritional guidance, behavioral modification, and exercise counseling throughout the study. All patients began multivitamin supplementation at the time of randomization.

NUMBER OF SUBJECTS - 539 randomized

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION - Males and females between 12 and 16 years of age with a body mass index (BMI) at the time of screening that was 2 units greater than the US weighted mean for the 95th percentile based on age and gender were eligible for study entry.

DOSE / ROUTE / REGIMEN / DURATION - 120 mg/oral/tid/52 weeks

CRITERIA FOR EFFICACY EVALUATION - The primary efficacy parameter was change in BMI from baseline to the end of the study. The secondary efficacy parameters were change in body weight, total cholesterol, LDL cholesterol, HDL cholesterol, LDL/HDL ratio, triglycerides, diastolic and systolic blood pressure, waist circumference, and glucose and insulin responses to an oral glucose challenge. In addition, hip circumference and categorical changes in BMI and body weight were analyzed for the report.

STATISTICAL METHODS - Efficacy was analyzed for all patients who had baseline efficacy assessments and at least one post-baseline efficacy measurement (ITT population). Primary and secondary efficacy endpoints were also analyzed for all patients who completed a final visit at week 52 (Completers population). All efficacy endpoints were derived using the last-observation-carried-forward (LOCF) data set. Change from baseline to week 52 in BMI was analyzed using an analysis of covariance model (ANCOVA) that included change from baseline value as the response, and treatment, center, and treatment-by-center, and baseline stratification terms.

METHODOLOGY: Patients meeting the inclusion criteria were entered into the study and, after a 2-week placebo lead-in period, were randomized to receive either orlistat or placebo in a 2:1 ratio. Patients were instructed to take their study medication 3 times a day with meals and a multivitamin once a day 2 hours after a meal or at bedtime. All patients were maintained on a nutritionally balanced

hypopcaloric diet and provided with behavioral modification and exercise counseling.

EFFICACY RESULTS: Least squares mean (LSM) difference from placebo for the orlistat treatment group for BMI was -0.86 kg/m^2 at week 52. This difference between treatment groups was statistically significant (p= 0.001). The LSM difference from placebo for the orlistat treatment group for body weight was -2.61 kg at week 52 and this was also statistically significant (p= 0.001). Overall, 26.5% of orlistat-treated patients and 15.7% of placebo-treated patients had a 5% reduction of their baseline BMI and 13. 3% of orlistat-treated patients and 4.5% of placebo-treated patients had a 10% reduction of their baseline BMI. The difference between treatment groups for both BMI categories was statistically significant (p = 0.005 and p = 0.002, respectively). Similarly, significantly more patients treated with orlistat had 5% (19%) and a 10% (9.5%) reduction in baseline body weight than patients treated with placebo (11.7% of patients had a 5% weight loss and 3.3% of patients had a 10% weight loss; p-value for difference from orlistat-treated patients is 0.032 and 0.011, respectively). Since very few patients in this study had abnormalities in serum lipid values at baseline, it was not unexpected that there were no significant improvements by the end of the study and no significant differences between orlistat-treated and placebo-treated patients. Similarly, most of the patients in this study had normal glucose tolerance at baseline and patients in both treatment groups had similar decreases in mean 0 minute and 120 minute glucose values by the end of the study. Patients in both treatment groups also had large decreases in baseline insulin levels at the end of the study and there was no statistical difference between the treatment groups. Patients treated with orlistat had statistically significant reductions in both waist circumference (p= 0.008) and hip circumference (p= 0.013) compared with patients treated with placebo.

CONCLUSIONS: Orlistat when administered at a dose of 120 mg tid for 52 weeks in conjunction with a reduced calorie diet, exercise, and behavioral modification results in significant improvement in weight management for obese adolescent patients. In addition, orlistat is generally well tolerated in this patient population.

DATA ANALYZED AND SOURCES

Data used by the reviewer are from the electronic document room: electronic documents room): \\ CDSESUB1\N20766\S_018\2003-08-19

STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY

2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

Note: The sponsor's results and conclusions are following. To re-emphasize, Sections 2.1 to 2.3.2 are almost verbatim from the sponsor's submission. This reviewer's findings have been presented at appropriate places. His silence in Sections 2.1 to 2.3.2 does not imply agreement with the sponsor's statements (his comments, if any, are in italic as notes).

Note: Statistical review and analyses have been done by the reviewer only with respect to the primary efficacy evaluation: Change From Baseline in Body Mass Index (BMI).

Sponsor's Results (Body Mass Index)

The primary efficacy parameter for this study was change from baseline in BMI. During the first 12 weeks of treatment, patients in both groups had a decrease in BMI. During the rest of the treatment period, this decrease stabilized in the orlistat group, but increased to above baseline values in the placebo group (Figure below). By the end of the study, the BMI of patients treated with orlistat had decreased 0.62 kg/m^2 from baseline while the BMI of patients treated with placebo increased 0.17 kg/m^2 from baseline (the Table below the Figure).

Change of BMI (kg/m^2) from Baseline, LOCF Data, ITT Population:

	Within Treatment			Difference from Placebo				
	N	MEAN BASELINE VALUE	LS MEAN CHANGE FROM BASELINE	LS MEAN	SE	95% CI LOWER	95% CI UPPER	P-VALUE*
TREATMENT								
PLACEBO	178	35.49	0.31					
ORLISTAT	347	35.67	-0.55	-0.86	0.25	-1.34	-0.37	0.001

Figure for Mean Percent Change from Baseline BMI, LOFC, ITT:

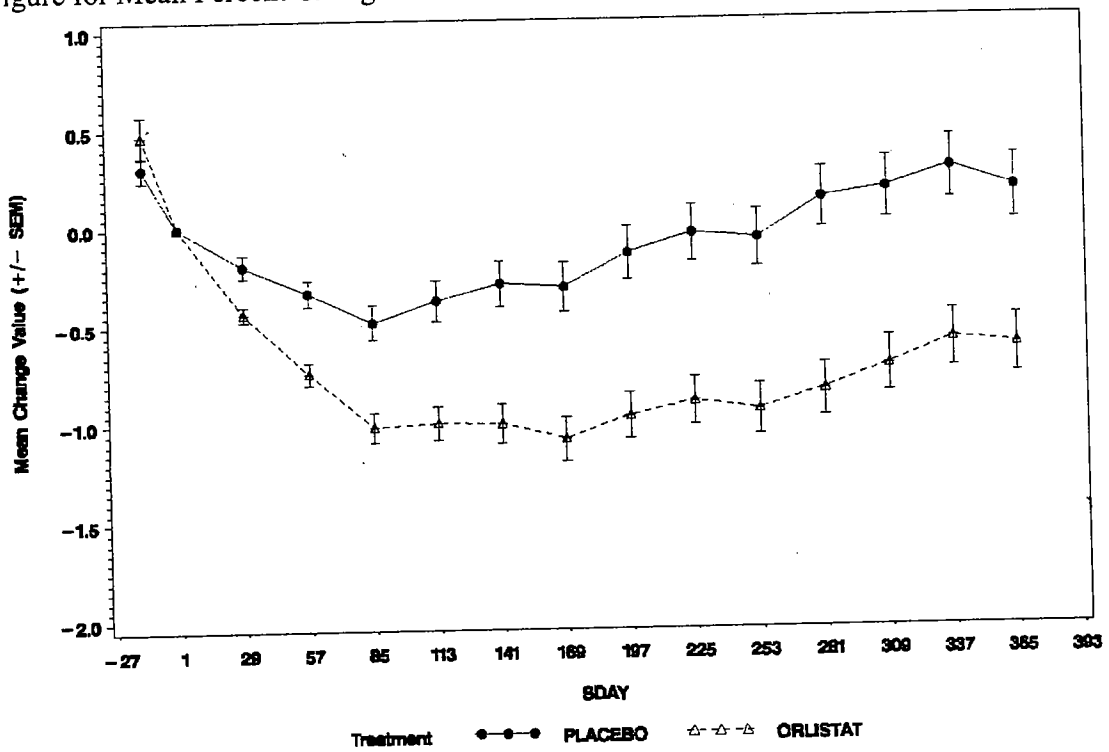


Table for Summary of BMI (kg/m^2), LOCF Data, ITT Population:

		Value at Scheduled Visit				Change from Baseline				% Change from Baseline			
PARAMETER	VISIT	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN
PLACEBO	DAY -14	179	35.74	3.92	35.20	179	0.30	0.87	0.40	179	0.94	2.48	0.96
	BASELINE	180	35.47	4.07	34.60								
	DAY 29	155	35.35	4.10	34.30	155	-0.20	0.73	-0.10	155	-0.55	2.10	-0.31
	DAY 57	177	35.19	4.22	34.20	177	-0.33	0.89	-0.30	177	-0.97	2.50	-0.98
	DAY 85	178	35.00	4.31	34.20	178	-0.49	1.17	-0.35	178	-1.40	3.31	-1.04
	DAY 113	178	35.11	4.42	34.25	178	-0.38	1.38	-0.30	178	-1.11	3.91	-0.83
	DAY 141	178	35.19	4.41	34.40	178	-0.29	1.55	-0.10	178	-0.85	4.35	-0.28
	DAY 169	178	35.17	4.56	34.40	178	-0.31	1.69	-0.20	178	-0.94	4.76	-0.52
	DAY 197	178	35.34	4.64	34.45	178	-0.14	1.81	0.00	176	-0.47	5.09	0.00
	DAY 225	178	35.44	4.68	34.35	178	-0.05	1.91	0.05	176	-0.19	5.33	0.12
	DAY 253	178	35.42	4.76	34.35	178	-0.07	1.94	0.00	178	-0.28	5.43	0.00
	DAY 281	178	35.62	4.75	34.65	178	0.13	2.01	0.20	178	0.31	5.59	0.64
	DAY 309	178	35.66	4.82	34.45	178	0.18	2.09	0.40	178	0.42	5.79	1.03
	DAY 337	178	35.76	4.86	34.80	178	0.28	2.16	0.35	178	0.71	6.02	0.97
	DAY 365	178	35.66	4.84	34.45	178	0.17	2.18	0.30	178	0.43	6.06	0.88
ORLISTAT	DAY -14	348	36.14	4.22	35.40	348	0.47	2.00	-0.40	348	1.47	6.38	1.05
	BASELINE	348	35.68	4.12	35.30								
	DAY 29	321	35.33	4.06	35.00	321	-0.44	0.70	-0.40	321	-1.22	1.99	-1.30
	DAY 57	344	34.94	4.11	34.75	344	-0.74	1.08	-0.70	344	-2.05	3.45	-1.94
	DAY 85	347	34.65	4.25	34.60	347	-1.02	1.38	-0.90	347	-2.85	4.23	-2.59
	DAY 113	347	34.67	4.35	34.60	347	-1.00	1.60	-0.80	347	-2.81	4.85	-2.28
	DAY 141	347	34.67	4.46	34.60	347	-1.00	1.88	-0.80	347	-2.81	5.58	-2.21
	DAY 169	347	34.59	4.55	34.60	347	-1.08	2.05	-0.70	347	-3.05	6.11	-2.21
	DAY 197	347	34.70	4.60	34.60	347	-0.97	2.18	-0.60	347	-2.72	6.46	-1.77
	DAY 225	347	34.77	4.66	34.70	347	-0.90	2.26	-0.60	347	-2.52	6.71	-1.65
	DAY 253	347	34.73	4.75	34.70	347	-0.94	2.39	-0.60	347	-2.66	7.09	-1.60
	DAY 281	347	34.83	4.78	34.80	347	-0.84	2.51	-0.40	347	-2.37	7.42	-1.23
	DAY 309	347	34.95	4.86	34.80	347	-0.72	2.62	-0.40	347	-2.03	7.69	-1.05
	DAY 337	347	35.08	4.90	34.90	347	-0.59	2.66	-0.30	347	-1.68	7.80	-0.88
	DAY 365	347	35.05	4.98	34.70	347	-0.62	2.73	-0.40	347	-1.78	7.99	-1.01

Sponsor's Conclusions

The results of this study indicate that orlistat, when administered at a dose of 120 mg tid for 52 weeks in conjunction with a reduced calorie diet, exercise, and behavioral modification results in a significant improvement in weight management for obese adolescent patients. In addition, orlistat is generally well tolerated in this patient population and no new findings were noted that were not previously identified in the adult population.

2.3.2 STATISTICAL METHODOLOGIES (Stated by the sponsor)

The following summary was based on the study protocol:

Since the body weight at randomization (the end of the lead-in period) and the amount of weight loss during the lead-in period are used to stratify patients within each center, an analysis of variance model will be performed, including the terms stratuml, center, stratum2, treatment, center*treatment, body weight at randomization and weight loss during the lead-in period as covariates. In the event of missing strata, an analysis of covariance will be used with covariates

Note: See Section 2.33.1.5 Efficacy Results (Sponsor's Analyses) for more details.

2.3.3 DETAILED REVIEW OF INDIVIDUAL STUDIES

Only one Phase III study, **Study MA-98-0108** (U.S.), as presented in Tabular form in Section 1.2 "Overview of Clinical Program and Studies Reviewed", has been conducted for this indication.

2.3.3.1 Study NM16189

2.3.3.1.1 Primary Objective

To characterize the efficacy of Xenical administered daily (120 mg TID with meals) as an adjunct to diet in the treatment of obese pediatric patients.

2.3.3.1.2 Disposition of Patients

A total of 539 patients from 32 centers were randomized. Of these 539 patients, 182 were randomized to the placebo group and 357 were randomized to the orlistat group. A similar percentage of patients in each treatment group (placebo, 64%; orlistat 65%) completed the study. A total of 11 patients were excluded from the ITT analysis population because they did not have a follow-up efficacy assessment (Table below). In addition, six patients were excluded from the safety population because they did not have a follow-up safety assessment.

A summary of the percentage of patients in each analysis population is presented in Table below:

	PLACEBO	ORLISTAT
No. of Patients Randomized	182	357
No. Included in ITT	180	348
No. Excluded from ITT	2	9
No. Included in SAFETY	181	352
No. Excluded from SAFETY	1	5

Summary of Reasons for Premature Withdrawal from Study:

Reason for Withdrawal	PLACEBO N = 181 No. (%)	ORLISTAT N = 352 No. (%)
Safety	3 (2)	12 (3)
Abnormality of Laboratory Test	0	0
Adverse Event(a)	3	12
Death	0	0
Nonsafety	61 (34)	108 (31)
Insufficient Therapeutic Response	1	3
Violation of Selection Criteria at Entry	1	1
Other Protocol Violation	3	2
Refused Treatment(b)	31	68
Failure to Return	23	28
Other	2	6
Total	64 (35)	120 (34)

(a)=Including intercurrent illness (b)=Including 'did not co-operate', 'withdrew consent'
Percentages are based on N. Percentages not calculated if N < 10.

"The Failure to Return" rate was much higher in the placebo group.

Figure for Percent of Patients Continuing in the Trial Over Time:

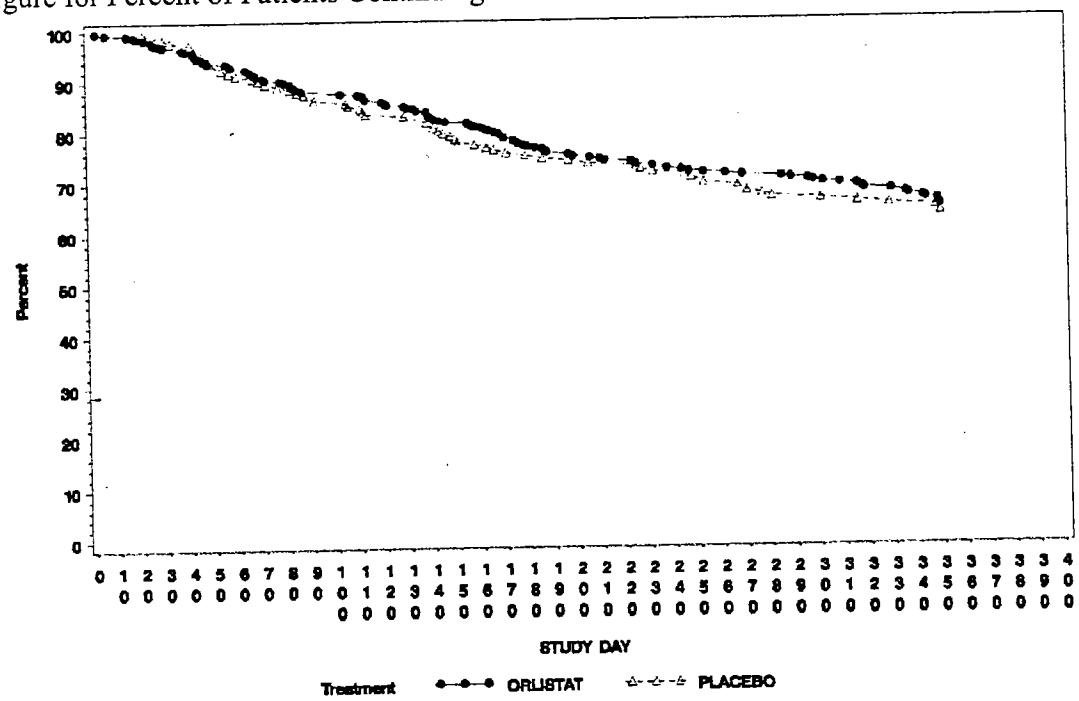


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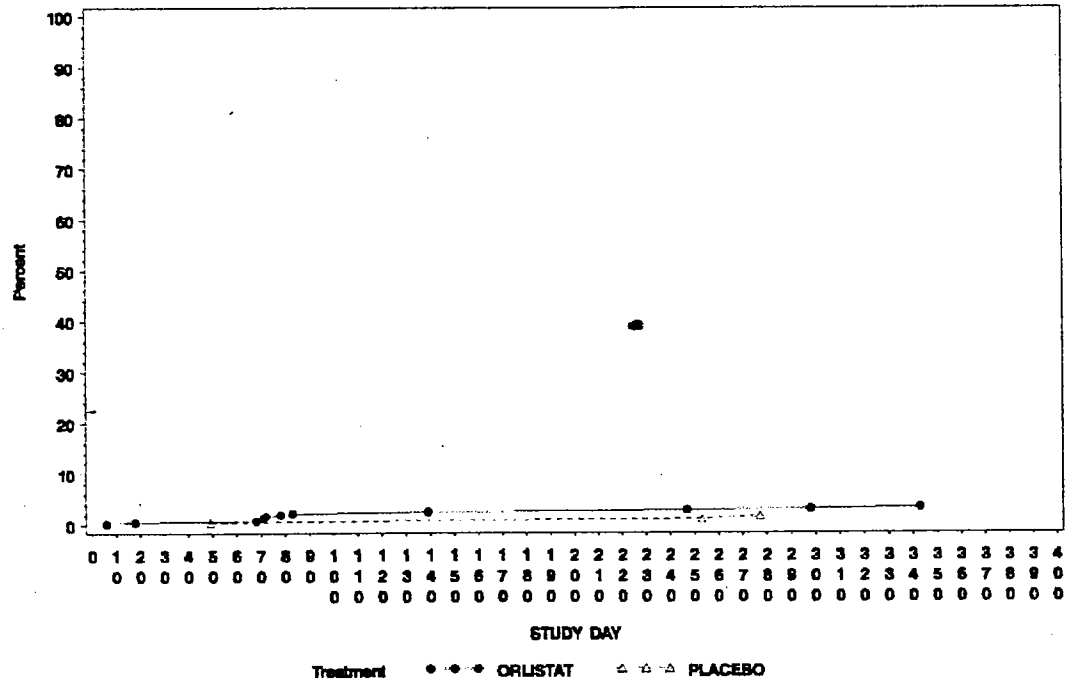
Figure for Percent of Patients Withdrawn from Trial Due to Adverse Events Over Time:



2.3.3.1.3 Demographic and Other Baseline Characteristics

Demographic characteristics were generally similar in the placebo and orlistat treatment groups for all analysis populations (Table below). Most of the patients were Caucasian and there were slightly more girls than boys enrolled in both treatment groups. Patients in both treatment groups were also assigned to a similar diet (2nd Table below).

The patients in the orlistat treatment group had a slightly higher mean body weight than patients in the placebo group. Randomization strata were based on baseline body weight and weight loss during the placebo lead-in period. Although this randomization plan successfully balanced the treatment groups regarding these parameters, overall a larger percentage of patients had a baseline body weight ≥80 kg and the mean number of patients in this body weight group was slightly higher in the orlistat treatment group than in the placebo group.

Although there was a slight difference between treatment groups in body weight, the mean BMI was similar in both groups at approximately 35 kg/m^2. The patients in this study were above the 98th percentile for BMI. These patients are similar to morbidly obese adults who are known to be the most resistant to treatment.

The patients in the orlistat treatment group had a slightly higher mean height and mean waist circumference than patients in the placebo group. Statistical analyses (submission dated August 26, 2003) showed that these and body weight were not significant predictors of response and, therefore, imbalances in them should not be of much concern.

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Summary of Demographic Data, ITT Population:

PARAMETER	PLACEBO	ORLISTAT
SEX		
MALE	52 (28.7)	124 (35.2)
FEMALE	129 (71.3)	228 (64.8)
TOTAL	181 (100.0)	352 (100.0)
RACE		
CAUCASIAN	141 (77.9)	264 (75.0)
BLACK	25 (13.8)	66 (18.8)
OTHER	15 (8.3)	22 (6.3)
TOTAL	181 (100.0)	352 (100.0)
BW PRELOSS		
BW PRELOSS <1%	95 (52.5)	166 (47.2)
BW PRELOSS >=1%	86 (47.5)	186 (52.8)
ALL	181 (100.0)	352 (100.0)
BL BW		
BL BW <80 kg	22 (12.2)	36 (10.2)
BL BW >=80 kg	159 (87.8)	316 (89.8)
ALL	181 (100.0)	352 (100.0)
AGE		
N	181	352
MEAN	13.50	13.61
SD	1.24	1.35
MEDIAN	13.00	13.00
MIN,MAX	11.00,16.00	11.00,16.00
95% C.I.	13.32,13.68	13.47,13.76
WEIGHT (kg)		
N	181	352
MEAN	95.11	97.71
SD	14.18	14.96
MEDIAN	93.90	96.85
MIN,MAX	60.60,134.10	58.10,133.00
95% C.I.	93.03,97.19	96.14,99.28
HEIGHT (cm)		
N	181	352
MEAN	163.65	165.16
SD	7.74	8.43
MEDIAN	163.00	165.00
MIN,MAX	143.00,190.00	141.00,191.00
95% C.I.	162.51,164.78	164.28,166.05
BMI (kg/m^2)		
N	181	352
MEAN	35.43	35.72
SD	4.07	4.17
MEDIAN	34.60	35.20
MIN,MAX	27.30,45.40	24.00,46.60
95% C.I.	34.83,36.03	35.28,36.16

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PARAMETER	PLACEBO	ORLISTAT
HEIGHT PERCENTILE*		
N	180	348
MEAN	64.04	66.33
SD	26.29	27.14
MEDIAN	70.28	72.66
MIN,MAX	1.56,99.99	1.55,99.99
95% C.I.	60.17,67.90	63.47,69.19
WEIGHT PERCENTILE*		
N	180	348
MEAN	98.97	99.08
SD	1.21	1.13
MEDIAN	99.31	99.46
MIN,MAX	91.82,99.99	92.29,99.99
95% C.I.	98.79,99.15	98.96,99.20
BMI PERCENTILE*		
N	180	348
MEAN	98.86	98.89
SD	0.72	1.02
MEDIAN	99.07	99.10
MIN,MAX	96.41,99.74	84.53,99.80
95% C.I.	98.76,98.97	98.78,98.99

Summary and Confidence Intervals for Study Caloric Intake Assignment, ITT Population:

Parameter	Treatment Group	Value at Screening Visit						Difference from Placebo 95% Confidence Interval	
		N	Mean	SD	Median	Min	Max	Lower Limit	Upper Limit
Calories from Carbohydrates									
	PLACEBO	180	770	122	800	250	990		
	ORLISTAT	346	793	92	800	260	990	-6.6	28.7
Calories from Fat									
	PLACEBO	180	464	49	450	280	700		
	ORLISTAT	346	470	55	480	280	900	-6.7	10.8
Calories from Protein									
	PLACEBO	180	316	92	300	210	900		
	ORLISTAT	346	314	67	320	180	900	-16.9	12.2
Total Daily Calories									
	PLACEBO	180	1549	145	1500	1200	1810		
	ORLISTAT	346	1577	148	1600	1200	1800	-10.5	32.3

Very few patients in this study had risk factors associated with obesity at baseline other than waist circumference and hyperinsulinemia, and very few patients had impaired glucose tolerance or were diabetic (Table 13 and Table 14 in the sNDA). Almost all of the girls in both the placebo and orlistat treatment groups had a baseline waist

circumference ≥84 cm. A higher percentage of boys in the orlistat treatment group (78%) compared with the placebo treatment group (71%) had a baseline waist circumference ≥102 cm. A slightly higher percentage of orlistat-treated patients (74%) compared with placebo-treated patients (69%) had hyperinsulinemia at baseline.

All of the patients in both treatment groups received concomitant medications during the study (page 180). Mild analgesics were the most frequently reported concomitant medication in both treatment groups with 51% of patients in the placebo group and 60% of patients in the orlistat group reporting taking these medications. This difference is mainly accounted for by the use of paracetamol (orlistat, 52%; placebo 44%). A slightly higher percentage of patients in the orlistat group (55%) reported taking anti-inflammatory agents than patients in the placebo group (49%), with the difference mainly accounted for by the use of ibuprofen (orlistat, 51%; placebo 45%). A patient listing of previous and concomitant medications is available upon request (Study Population Section, see page 1081).

2.3.3.1.4 Measurements of Treatment Compliance and Other Factors That Could Affect Response

Extent of Exposure to Trial Medication:

Overall, 65% of orlistat- treated patients and 63% of placebo- treated patients were treated for 52 weeks (Table below). The calculated compliance based on pill count was 73% in the orlistat treatment group and 72% in the placebo treatment group.

	PLACEBO N = 181 No. (%)	ORLISTAT N = 352 No. (%)
ORLISTAT		
Treatment Duration (days)		
1 - 42	1 (<1)	18 (5)
43 - 70	-	15 (4)
71 - 98	1 (<1)	12 (3)
99 - 140	-	18 (5)
141 - 196	-	26 (7)
197 - 252	-	16 (5)
253 - 316	-	19 (5)
317 - 420	-	228 (65)
Total Cumulative Dose (MG)		
Mean	16200.0	161751.5
SD	21382.91	79961.91
SEM	15120.00	4261.98
Median	16200.0	144720.0
Min	1080	1440
Max	31320	294480
n	2	352

PLACEBO

Treatment Duration (days)		
1 - 42	7 (4)	6 (2)
43 - 70	15 (8)	-
71 - 98	8 (4)	-
99 - 140	4 (2)	-
141 - 196	15 (8)	-
197 - 252	8 (4)	-
253 - 316	10 (6)	-
317 - 420	114 (63)	-

2.3.3.1.5 Efficacy Results (Sponsor's Analyses)

The protocol stated:

> The primary efficacy variable for this study is BMI. Throughout the study, the patient's body weight and height will be recorded at every visit to the clinic (Appendix 3).
>
> Because these adolescent patients may experience linear growth during the study, the actual body weight may remain the same while the BMI may change by the end of the study. Therefore, change from baseline in BMI will be presented.
>
> The primary efficacy parameter will be presented as absolute change and percent (%) change.
>
> Ho: The mean BMI change is the same between patients in both the placebo and Xenical treatment groups.
>
> Descriptive statistics will be provided for all changes in primary and secondary efficacy parameters (mean, median, standard error).
>
> Since the body weight at randomization (the end of the lead-in period) and the amount of weight loss during the lead-in period are used to stratify patients within each center, an analysis of variance model will be performed, including the terms stratuml, center, stratum2, treatment, center*treatment, body weight at randomization and weight loss during the lead-in period as covariates. In the event of missing strata, an analysis of covariance will be used with covariates weight loss during the lead-in period and baseline weight.
>
> For the analysis of primary efficacy, an intent-to-treat (ITT) population consisting of all randomized patients who have received at least one dose of study medication and have a follow-up visit for BMI will be used.

In addition to the last observation carried forward approach, a per-protocol analysis will be provided using patients who have completed the study and have had a measurement of the parameter of interest at week 52.

There was a Statistical Analysis Plan (SAP). However, its purpose is not clear, when it was even less detailed than the protocol. August 26, 2003 submission states that small modifications such as adjustment of time windows, etc. were made. SAP was finalized on Oct. 28, 2002, data base was closed on the same date, and data base was unblinded on Nov. 4, 2002.

A paragraph from the SAP reads, "The primary statistical analysis will use ANCOVA methods with change in BMI as the response variable. The model will be: / ——— / / ——— / One strata is based on whether or not a patient weighed 80 kgs, and the other was based on whether or not they lost 1 kg during the two week lead in. In the event of missing strata, baseline body weight, and pre-loss will be treated as quantitative covariates. To avoid estimability complications, centers with missing cells will be collapsed into one center."

§ Results: Primary Efficacy Parameter (Body Mass Index)

The primary efficacy parameter for this study was change from baseline in BMI. During the first 12 weeks of treatment, patients in both groups had a decrease in BMI. During the rest of the treatment period, this decrease stabilized in the orlistat group, but increased to above baseline values in the placebo group (Figure below). By the end of the study, the BMI of patients treated with orlistat had decreased 0.62 kg/m^2 from baseline while the BMI of patients treated with placebo increased 0.17 kg/m^2 from baseline (2nd Table below).

Table for Summary of BMI (kg/m^2), LOCF Data, ITT Population:

	Within Treatment			Difference from Placebo				
TREATMENT	N	MEAN BASELINE VALUE	LS MEAN CHANGE FROM BASELINE	LS MEAN	SE	95% CI LOWER	95% CI UPPER	P-VALUE*
PLACEBO	178	35.49	0.31					
ORLISTAT	347	35.67	-0.55	-0.86	0.25	-1.34	-0.37	0.001

Change of BMI (kg/m^2) from Baseline, LOCF Data, ITT Population:

		Value at Scheduled Visit				Change from Baseline				% Change from Baseline			
PARAMETER	VISIT	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN	N	MEAN	SD	MEDIAN
PLACEBO	DAY -14	179	35.74	3.92	35.20	179	0.30	0.87	0.40	179	0.94	2.48	0.96
	BASELINE	180	35.47	4.07	34.60								
	DAY 29	155	35.35	4.10	34.30	155	-0.20	0.73	-0.10	155	-0.55	2.10	-0.31
	DAY 57	177	35.19	4.22	34.20	177	-0.33	0.89	-0.30	177	-0.97	2.50	-0.98
	DAY 85	178	35.00	4.31	34.20	178	-0.49	1.17	-0.35	178	-1.40	3.31	-1.04
	DAY 113	178	35.11	4.42	34.25	178	-0.38	1.38	-0.30	178	-1.11	3.91	-0.83
	DAY 141	176	35.19	4.41	34.40	178	-0.29	1.55	-0.10	178	-0.85	4.35	-0.28
	DAY 169	178	35.17	4.56	34.40	178	-0.31	1.69	-0.20	178	-0.94	4.76	-0.52
	DAY 197	178	35.34	4.64	34.45	178	-0.14	1.81	0.00	178	-0.47	5.09	0.00
	DAY 225	178	35.44	4.68	34.35	178	-0.05	1.91	0.05	178	-0.19	5.33	0.12
	DAY 253	178	35.42	4.76	34.35	178	-0.07	1.94	0.00	178	-0.28	5.43	0.00
	DAY 281	178	35.62	4.75	34.65	178	0.13	2.01	0.20	178	0.31	5.59	0.64
	DAY 309	178	35.66	4.82	34.45	178	0.18	2.09	0.40	178	0.42	5.79	1.03
	DAY 337	178	35.76	4.86	34.80	178	0.28	2.16	0.35	178	0.71	6.02	0.97
	DAY 365	178	35.66	4.84	34.45	178	0.17	2.18	0.30	178	0.43	6.06	0.88
ORLISTAT	DAY -14	348	36.14	4.22	35.40	348	0.47	2.00	0.40	348	1.47	6.38	1.05
	BASELINE	348	35.68	4.12	35.30								
	DAY 29	321	35.33	4.06	35.00	321	-0.44	0.70	-0.40	321	-1.22	1.99	-1.30
	DAY 57	344	34.94	4.11	34.75	344	-0.74	1.08	-0.70	344	-2.05	3.45	-1.94
	DAY 85	347	34.65	4.25	34.60	347	-1.02	1.38	-0.90	347	-2.85	4.23	-2.59
	DAY 113	347	34.67	4.35	34.60	347	-1.00	1.60	-0.80	347	-2.81	4.85	-2.28
	DAY 141	347	34.67	4.46	34.60	347	-1.00	1.88	-0.80	347	-2.81	5.58	-2.21
	DAY 169	347	34.59	4.55	34.60	347	-1.08	2.05	-0.70	347	-3.05	6.11	-2.21
	DAY 197	347	34.70	4.60	34.60	347	-0.97	2.18	-0.60	347	-2.72	6.46	-1.77
	DAY 225	347	34.77	4.66	34.70	347	-0.90	2.26	-0.60	347	-2.52	6.71	-1.65
	DAY 253	347	34.73	4.75	34.70	347	-0.94	2.39	-0.60	347	-2.66	7.09	-1.60
	DAY 281	347	34.83	4.78	34.80	347	-0.84	2.51	-0.40	347	-2.37	7.42	-1.23
	DAY 309	347	34.95	4.86	34.80	347	-0.72	2.62	-0.40	347	-2.03	7.69	-1.09
	DAY 337	347	35.08	4.90	34.90	347	-0.59	2.66	-0.30	347	-1.68	7.80	-0.88
	DAY 365	347	35.05	4.98	34.70	347	-0.62	2.73	-0.40	347	-1.78	7.99	-1.01

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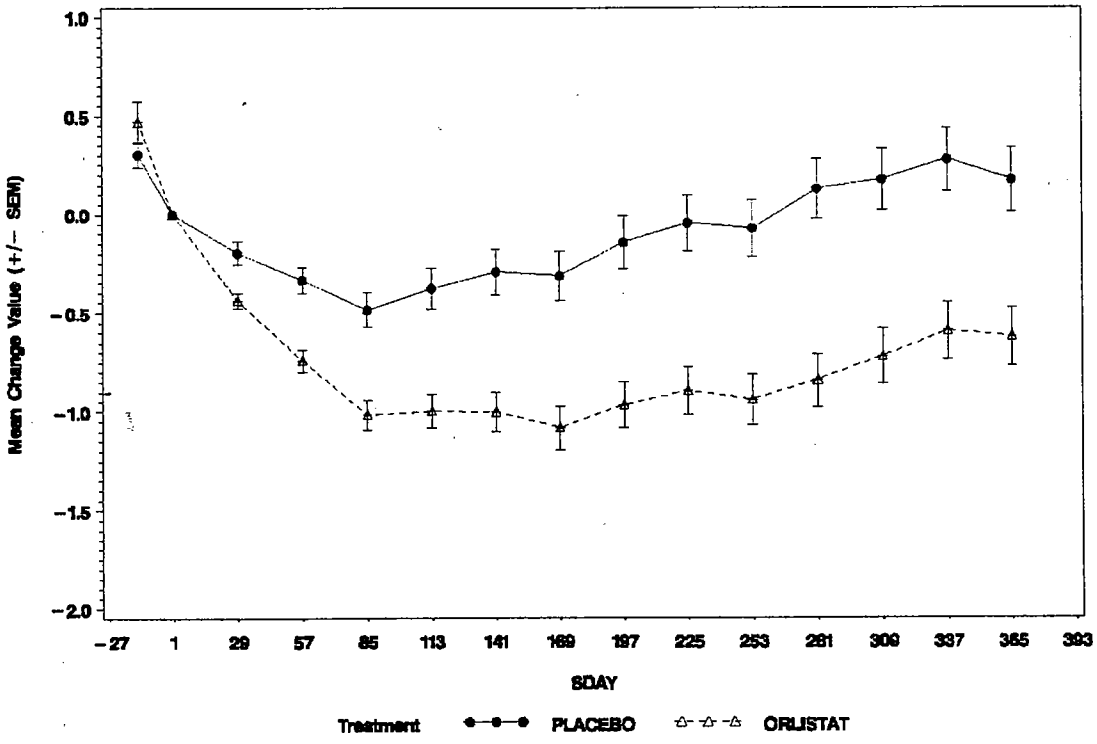
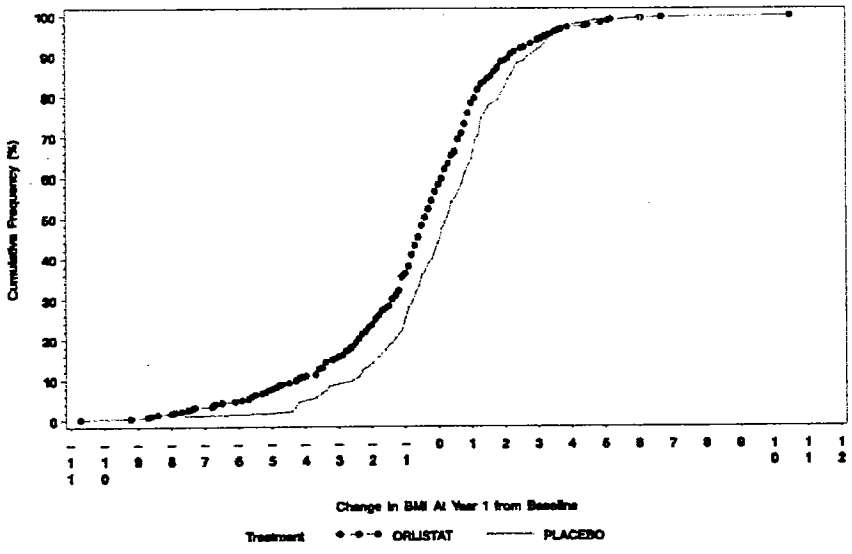
Figure for Mean Percent Change from Baseline BMI, LOFC, ITT:



Following is the cumulative distribution graph for BMI Change from Baseline, at Year 1, ITT, LOCF:

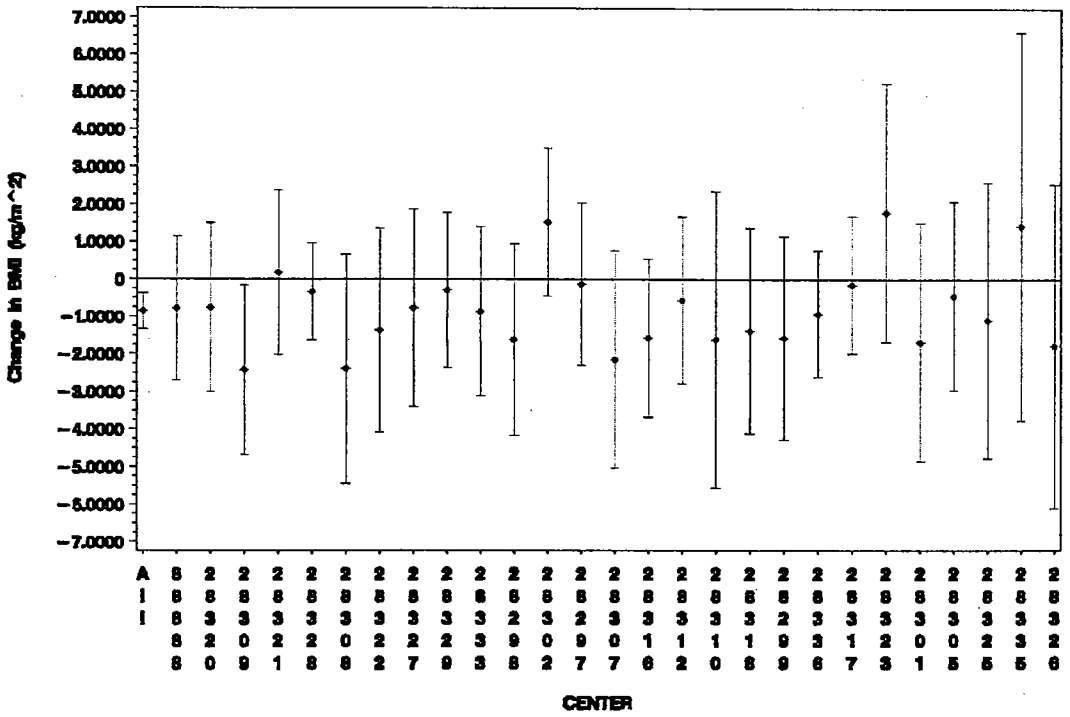


From this, percent of patients (y-axis value) with a value of Change from Baseline, smaller than or equal to a value on the x-axis can be read. For example, roughly 45% of the placebo patients had a ≤0 change from baseline compared with roughly 60% of patients in the orlistat group with that change. The median for placebo was .3 compared with -.4 for orlistat.

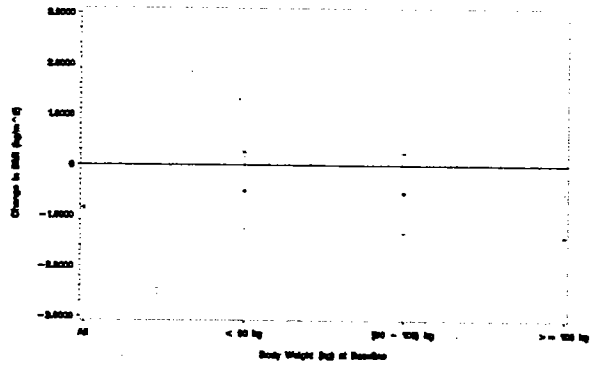
§ The sponsor stated (page 52), "Using SAS Proc Mixed, the results for BMI differed marginally by center (p = 0.0862) and significantly by treatment (p = 0.0006) (Table 16 in the sNDA). However, there was no center by treatment interaction indicating that treatment behaved the same across centers (interaction p = 0.8191). In addition, baseline body weight and body weight pre-loss did not significantly effect the change in BMI."

The corresponding 95% confidence intervals follow, where we see that in four out of 27 centers (one is formed by combining small centers) placebo did better than orlistat. However, this did not lead to a significant center by treatment interaction as mentioned before.

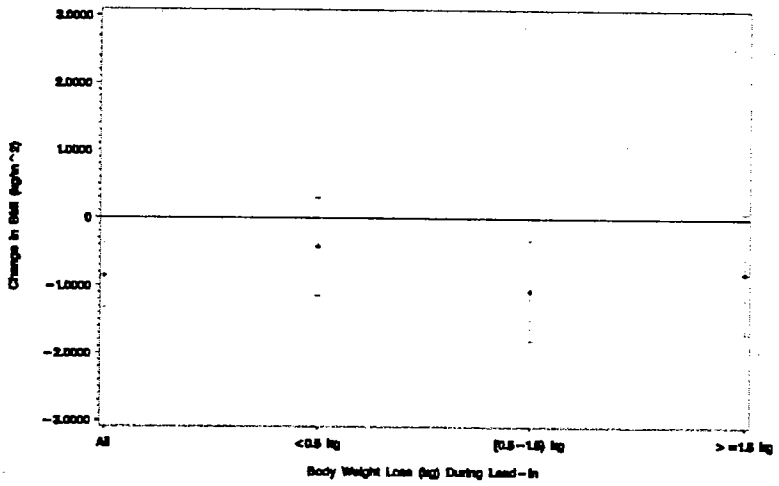
95% Confidence Intervals for difference from Placebo in LSMs by Center



95% Confidence Intervals for difference from Placebo in LSMs, by Body Weight at Baseline



95% Confidence Intervals for difference from Placebo in LSMs, by Body Weight Loss during Placebo Lead-In Period



§ The LSM change from baseline to end of treatment was –0.38 kg/m^2 for female patients treated with orlistat and 0.19 kg/m^2 for female patients treated with placebo and this difference was statistically significant (p = 0.048).

The LSM change from baseline to the end of treatment was -1.08 kg/m^2 for male patients treated with orlistat and 0.15 kg/m^2 for male patients treated with placebo (p = 0.004).

The Gender by treatment p-value was non-significant (.1965, 9-25-03 submission).

§ Black patients treated with orlistat had less of an increase in BMI and gained less weight by the end of the study than black patients treated with placebo, although the differences were not statistically significant (25 patients in placebo and 64 patients in orlistat, p=.207). The LSM change from baseline to the end of treatment for BMI was 0.10 kg/m^2 for black patients treated with orlistat and 0.74 kg/m^2 for black patients treated with placebo. For white patients the corresponding LSM change from baseline to the end of treatment for BMI was -0.72 kg/m^2 for patients treated with orlistat and 0.06 kg/m^2 for patients treated with placebo (138 patients in placebo and 261 patients in orlistat, p=.005).

The Race (3 categories, including "Other") by treatment interaction p-value was non-significant (.4089, 9-25-03 submission).

§ For boys and girls in the study who were prepubertal (Tanner stage 1 through 4) at screening, the LSM change from baseline to the end of the study for BMI was -0.76 kg/m^2 for patients treated with orlistat and 0.18 kg/m^2 for patients treated with placebo (p = 0.001; Table 42 of the sNDA). For Tanner stage 5 patients, the corresponding LSM change from baseline to the end of the study for BMI was -0.65 kg/m^2 for patients treated with orlistat and 1.35 kg/m^2 for patients treated with placebo (p=.173, 9-25-03 submission).

The tanner stage by treatment interaction p-value was non-significant (.4686, 9-25-03 submission).

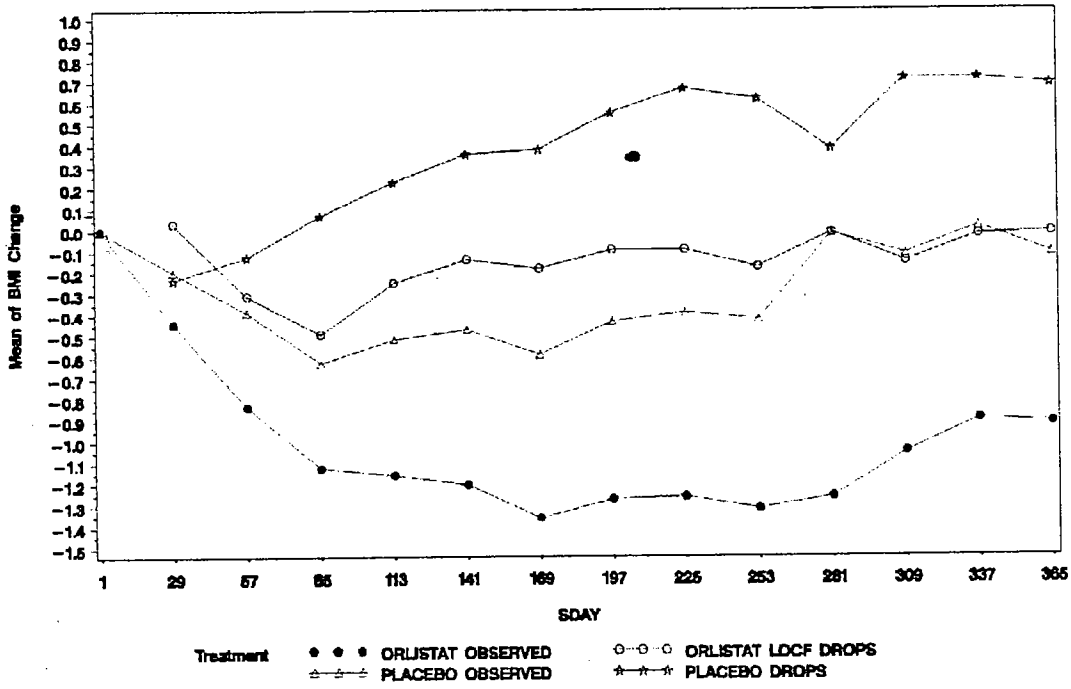
§ For patients aged ≤14 years, the LSM change from baseline to the end of the study for BMI was -0. 59 kg/m^2 for patients treated with orlistat and 0.24 kg/m^2 for patients treated with placebo (p = 0.001; Table 45 of the sNDA). For patients aged >14 years, the corresponding LSM change from baseline to the end of the study for BMI was -0.70 kg/m^2 for patients treated with orlistat and -0.03 kg/m^2 for patients treated with placebo (p= .211 9-25-03 submission).

The age by treatment interaction p-value was non-significant (.7912, 9-25-03 submission).

§ The patients in the orlistat treatment group had a slightly higher mean body weight, height, and waist circumference than patients in the placebo group. Statistical analyses (submission dated August 26, 2003) showed that these were not significant predictors of response and, therefore, marginal imbalances in them should not be of much concern. The sponsor stated, "Note that in every model …, the treatment group was found to be a significant predictor of change in BMI (p<. 001)."

The pre-specified covariates body weight at baseline and weight loss during the lead-in period did not have statistically significant interaction (interaction p-values are .30 and .98, respectively) with treatment.

§ BMI mean change from baseline for (1) observed cases and (2) those of unobserved cases, using the last available observations:



As expected, the adolescents who remained in the study did better on average than those who dropped out. Furthermore, within each of these two cohorts the magnitude of the between group treatment difference was reasonably similar.

2.3.3.1.6 Reviewer's Comments and Conclusions on Study NM16189

Sponsor's analyses and this reviewer's alternative analyses based on data provided on 8-19-03 to the EDR for Study NM16189, have provided statistical evidence in favor of orlistat with respect to the primary efficacy variable change from baseline to the end of the study for BMI.

Japobrata Choudhury, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot

CC:
Archival sNDA 20766/SE5-018

HFD-510/Dr. Colman
HFD-510/Dr. Kehoe
HFD-700/ Dr. Anello
HFD-715/Dr. Nevius
HFD-715/Dr. Wilson
HFD-715/Dr. Sahlroot
HFD-715/Dr. Choudhury

J.Choudhury:7-3110: 11/12/03

This review consists of 25 pages of text.

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/s/

Japobrata Choudhury
11/13/03 01:57:23 PM
BIOMETRICS

Todd Sahlroot
11/13/03 02:15:22 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-766/S-018

Clinical Pharmacology and Biopharmaceutics Review

Executive Summary

Xenical® (orlistat) capsules, 120 mg, were approved for obesity management in April 1999. On June 23, 2003, the sponsor submitted this sNDA including two pediatric studies to fulfill the Pediatric Exclusivity Written Request. The two studies are listed as follows:

Protocol PP16203:
The effect of orlistat (Xenical, Ro 18-0647) on the balance of selected minerals in obese pediatric and adolescent patients.

Protocol NM16189:
A double-blind, placebo-controlled, 54-week study of the efficacy and safety of Xenical® (orlistat) in the weight management of obese pediatric patients.

In these studies, plasma concentrations of orlistat and its metabolites M1 and M3 at 2 to 4 hours post lunch dose were measured. In study PP16203, the effects of orlistat on mineral balance (calcium, copper, iron, magnesium, and zinc), plasma and urine sodium and potassium, urine creatinine, and fecal fat excretion were evaluated. Based on the study results, the sponsor proposed labeling changes including the Special Populations and Other Short-term Studies subsections of the CLINICAL PHARMCOLOGY section.

Results showed that the exposure to orlistat and its metabolites M1 and M3 in adolescent patients was similar to historical data in adults at the same dose level. Orlistat did not affect mineral balance of calcium, copper, magnesium, or zinc. Iron balance was decreased in both placebo and orlistat groups and there was more loss in the orlistat treatment group. Orlistat treated patients had increased daily fecal fat excretion (15.9 g/day or 27% dietary intake) relative to placebo-treated patients (4.1 g/day or 7% of dietary intake).

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/s/

Hae-Young Ahn
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OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-766/SE5 018	Submission Date(s): June 23, 2003; July 31, 2003; August 19, 2003; August 26, 2003; September 25, 2003
Brand Name	Xenical®
Generic Name	Orlistat
Reviewer	Wei Qiu, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPEII
ORM division	Division of Metabolic and Endocrine Drug Products
Sponsor	Hoffmann-La Roche Inc.
Submission Type	Phase IV Pediatric Study Reports
Formulation; Strength(s)	Capsules; 120 mg
Indication	Treatment of obesity

1 Executive Summary

Xenical® (orlistat) capsules, 120 mg, were approved for obesity management in April 1999. On June 23, 2003, July 31, 2003, August 19, 2003, August 26, 2003, September 25, 2003, the sponsor submitted this sNDA including two pediatric studies to fulfill the Pediatric Exclusivity Written Request. The two studies are listed as follows:

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1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 20-766/S-018 submitted on June 23rd, 2003, July 31, 2003, August 19, 2003, August 26, 2003, September 25, 2003 and finds it acceptable. Recommendation, comments, and labeling comments should be conveyed to the sponsor as appropriate.

1.2 Phase IV Commitments

Not applicable.

2 Table of Contents

3 Summary of CPB Findings

Plasma levels of orlistat and its metabolites M1 and M3

Adolescents exhibited similar plasma concentrations of orlistat, M1, and M3 at 2 to 4 hours post dose to historical data in adults.

After 21-day treatment with orlistat 120 mg tid, plasma concentrations of orlistat, M1 and M3 at 4 hours post lunch dose were 0.428, 32.7, and 117.2 ng/mL, respectively. It appeared that orlistat concentration at day 21 was lower than the previous days, while M1 and M3 appeared to accumulate after 21-day dosing.

In a multi-center 52 weeks study, patients were treated with orlistat 120 mg tid or placebo. Similar plasma concentrations of orlistat, M1 and M3 at 2 to 4 hours post lunch dose at day 141 and 337 were observed. It is consistent with the expectation that steady state was already achieved at day 141. Approximately 30 to 40% of samples had measurable orlistat concentration ranged from [redacted] while historical data showed that at the same dose level, measurable orlistat

concentration ranging from [redacted] were found in 40 to 60% adult patients. Plasma concentrations of M1 and M3 were [redacted], at day 141, [redacted] and [redacted] at day 337, respectively. Historical adult data showed that after 24 or 25 weeks treatment, M1 and M3 concentrations, on average, were 20 to 30 ng/mL and 70 to 107 ng/mL, respectively. The approved labeling stated that, at therapeutic dose, average concentrations of M1 and M3 at 2 to 4 hours after a dose were 26 ng/mL and 108 ng/mL, respectively.

Mineral balance (calcium, copper, iron, magnesium, and zinc)

For minerals including calcium, copper, magnesium, phosphorous and zinc, similar amount of mineral was ingested and excreted between day 15 and 22 in both the placebo and orlistat groups. However, iron balance was decreased by 64.7 µmole/24 hours and 40.4 µmole/24 hours in orlistat and placebo treatment groups, respectively. It appeared that there was more iron loss in orlistat treatment group.

Plasma and urine sodium and potassium and urine creatinine

Serum sodium, or potassium, or urine sodium concentrations at day 22 were comparable between placebo and orlistat treatment groups. Mean urine potassium concentrations were slightly lower in orlistat treatment group (43.0 mmole/L) than placebo group (60.0 mmole/L).

Similar urinary creatinine excretion was observed in both groups from day 15 to 22. The mean urinary creatinine excretions for placebo and orlistat groups were 1378 mg/24 hour and 1480 mg/24 hours, respectively.

Fecal fat excretion

Orlistat treated subjects had increased daily fecal fat excretion (15.9 g/24 hours or 27% of dietary intake) relative to placebo-treated subjects (4.1 g/24 hours or 7% of dietary intake).

4 QBR

4.1 General Attributes

Not applicable.

4.2 General Clinical Pharmacology

Not applicable.

4.3 Intrinsic Factors

Q1. What are the plasma concentrations of orlistat in children aged from 12 to 16 years old?

Plasma concentrations of orlistat and the two metabolites M1 and M3 at 4 hours post lunch dose after 21-day treatment with orlistat 120 mg tid doses were [redacted] respectively (Protocol PP16203).

When patients were administered 120 mg orlistat tid for 52 weeks (Protocol NM16189), approximately 30% to 40% of plasma samples at 2 to 4 hours post lunch dose at Day 141 and 337 had measurable orlistat concentrations ranged from [redacted] The remaining 60% to 70% of plasma samples had no measurable orlistat concentrations. M1 and M3 had the mean concentration of 20.15 ng/mL and 70.35 ng/mL on Day 141 and 14.49 ng/mL and 66.00 ng/mL

on Day 337, respectively. The exposure to adolscents were comparable to historical data obtained from adults.

Study PP16203 was a single-center, double-blind, placebo-controlled, randomized, multiple-dose, parallel-group study. Thirty-two adolescent patients were given 120 mg tid mid-meal for 21 days. Plasma concentrations of orlistat and its metabolites M1 and M3 at 4 hours post lunch dose after drug administration on days 1, 7, 14, and 21 were measured (**Table 1**). Not every subject had measurable orlistat in all plasma samples. It appears that mean orlistat plasma concentrations were lower at day 21 than previous days. However, metabolites M1 and M3 concentrations tend to increase.

Table 1. Plasma Concentrations of Orlistat and Orlistat Metabolites M1 and M3 at 4 hours post dose (Protocol PP 16203).

Day	Orlistat (ng/mL)		M1 (ng/mL)		M3 (ng/mL)	
	N*	Mean (SD)	N*	Mean (SD)	N*	Mean (SD)
1	14	0.774 (0.588)	16	26.4 (12.4)	15	44.8 (22.1)
7	13	0.696 (0.421)	16	24.2 (9.5)	16	93.2 (62.8)
14	13	0.869 (0.408)	16	25.1 (9.2)	16	102.2 (73.2)
21	11	0.428 (0.200)	15	32.7 (12.2)	15	117.2 (66.2)

*. Number of subjects whose samples had measurable concentrations.

Study NM16189 was a multicenter, randomized, double-blind, placebo-controlled, parallel study of obese adolescents. Patients were randomized to receive either 120 mg orlistat tid or placebo in a 2:1 ratio for 52 weeks. Five hundred and thirty nine adolescent patients were randomized. Plasma concentrations of orlistat and its metabolites M1 and M3 were collected at 2 to 4 hours after the lunch time dose at Day 141 and 337 (**Table 2**). It appears there was no further accumulation for orlistat or its metabolites M1 and M3 beyond 141 days. Steady state is expected to be achieved at day 141.

Table 2. Summary of Plasma Concentrations (ng/mL) of Orlistat and Its Metabolites M1 and M3 at 2-4 hours post lunch dose (Protocol NM16189)

Day of sample collection	Orlistat			M1		M3	
	No of samples	No of Meassurable*	% of Measurable	Mean (N)	SD	Mean (N)	SD
141	196	73	37.2	20.15 (174)	43.22	70.39 (169)	59.35
337	156	46	29.5	14.49 (127)	17.20	66.00 (115)	54.96

*With concentration range (ng/mL) in parentheses.

Approximately 30% to 40% of samples had measurable orlistat concentrations ranged from . On average, plasma M1 concentrations were 20.15 ng/mL and 14.49 ng/mL on day 141 and 337, respectively. Plasma M3 concentrations were 70.39 ng/mL and 66.00 ng/mL on day 141 and 337, respectively. Plasma levels of metabolite M1 and M3 were measurable in 70% to 90% of patients.

For comparison, adult data are extracted from literature (**Table 3**). With the same dose, comparable measurable concentrations ranged from were found in 40% to 60% adult obese patients. More than 90% adults had measurable M1 and M3 in plasma. The M1 and M3 concentrations are comparable between adults and adolescents.

Table 3. Summary of plasma concentration of orlistat and its metabolites M1 and M3 at 2-4 hours post either lunch or dinner dose with 120 mg tid doses (modified from Zhi J et al., J Clin Pharmacol 1999; 39:41-46).

Study No	Number of Samples	Orlistat		M1		M3	
		No of Measurable	% of Measurable	Mean (N)	SD	Mean (N)	SD
1	96	37	38	21.6 (94)	14.5	68.9 (91)	41.4
5	118	76	64	31.4 (115)	21.9	107 (101)	71

Study 1: Phase II, dose ranging study. Plasma samples were collected after 24 weeks of treatment. .
Study 5: Efficacy and tolerability in obese diabetics. Plasma samples were collected after 25 weeks treatment.

Q2. How does orlistat afftect mineral balance in children aged from 12 to 16 years old?

For calcium, copper, magnesium, phosphorous and zinc, comparable amount minerals were ingested and excreted between day 15 and 22 in both the placebo and orlistat groups. More iron was excreted than digested during a 24-hour period in both groups. Mean serum sodium, or potassium, or mean urine sodium levels at day 22 were similar between treatment groups (**Table 4**). However, it appears that orlistat treatment group had 17 mmole/L more urine potassium than placebo group. Over the 22-day course of the study, orlistat-treated subjects had increased daily fecal fat excretion (mean of 15.9 g/24 hour or 27% of dietary intake) relative to placebo-treated subjects (mean of 4.1 g/24 hour or 7% of dietary intake).

In Protocol PP16203, thirty-two patients were given 120 mg tid mid-meal for 21 days. The radio Opaque Markers were given 1 capsule tid mid-meal for 21 days. Mineral balances were calculated by [redacted] Fecal mineral content was normalized [redacted]

Mean fecal marker recovery was 70% for the placebo group and 69% for the orlistat treatment group. There was no difference in dietary intake of minerals between placebo and orlistat treatment groups. In placebo group, mean dietary intake of calcium, copper, iron, magnesium, phosphorus, and zinc were 35.0 mmole/24 hrs, 19.1 µmole/24 hrs, 341.9 µmole/24 hrs, 15.0 mmole/24 hrs, 52.5 mmole/24 hrs, and 322.2 µmole/24 hrs, respectively. In orlistat treatment group, mean dietary intake of calcium, copper, iron, magnesium, phosphorus, and zinc were 35.0 mmole/24 hrs, 19.1 µmole/24 hrs, 342.5 µmole/24 hrs, 15.0 mmole/24 hrs, 52.5 mmole/24 hrs, and 322.9 µmole/24 hrs, respectively.

For all minerals (calcium, copper, magnesium, phosphorus, and zinc), other than iron, similar amount of mineral was ingested and excreted during the 24 hour period in both the placebo and orlistat groups. However, both groups had decreases in mean iron balance while orlistat treatment group appeared to have more decrease than placebo group.

Table 4. Summary of Mean Mineral Balance Per 24 hours (From Day 15 to 22)

Mineral (per 24 hours)	Orlistat (n=14)				Placebo (n=13)			
	Mean	SE	Median	95% CI	Mean	SE	Median	95% CI
Calcium (mmole)	2.3	1.2	2.0	-0.4, 5.1	1.9	1.5	1.4	-1.0, 4.7
Copper (µmole)	0.6	0.7	-0.4	-0.7, 2.0	0.1	0.7	0.1	-1.4, 1.5
Iron (µmole)	-64.7	20.4	-49.7	-98.0, -31.4	-40.4	10.1	-32.9	-75.0, -5.9
Magnesium (mmole)	3.0	0.2	2.7	2.5, 3.5	2.7	0.2	2.3	2.2, 3.2
Phosphorus (mmole)	6.4	1.3	6.8	3.8, 9.1	5.8	1.3	4.1	3.1, 8.6
Zinc (µmole)	7.6	8.9	10.2	-7.5, 22.7	5.0	5.3	12.8	-10.6, 20.7

Mean serum sodium, or potassium, or mean urine sodium at day 22 were similar between groups (**Table 5**). Orlistat treatment group appeared to have lower urine potassium on average than placebo group.

Table 5. Summary of Serum and Urine Electrolytes

Electrolyte (mmole/L)	Orlistat					Placebo				
	N	Mean	SE	Median	95% CI	N	Mean	SE	Median	95% CI
Serum Sodium	15	142.4	0.4	142.0	141.7, 143.1	15	141.7	0.3	142.0	141.1, 142.4
Serum Potassium	15	4.1	0.1	4.1	4.0, 4.2	15	4.1	0.3	4.2	4.0, 4.3
Urine Sodium	14	113.4	9.3	107.5	88.7, 138.2	15	108.2	13.7	114.9	84.3, 132.0
Urine Potassium	14	43.0	4.6	37.8	30.7, 55.4	15	60.0	6.8	57.3	48.1, 71.9

Urinary creatinine excretion between groups during days 15 to 22 (placebo, 1378 mg/24 hour; orlistat, 1480 mg/24 hour) was similar.

Over the 22 day course of the study, orlistat-treated adolescent patients had increased daily fecal fat excretion (mean of 15.9 g/24 hour or 27% of dietary intake) relative to placebo-treated patients (mean of 4.1 g/24 hour or 7% of dietary intake) (**Table 6**).

Table 6. Summary of Fecal Fat Absorption

	Orlistat					Placebo				
	N	Mean	SE	Median	95% CI	N	Mean	SE	Median	95% CI
Dietary fat intake (g/24 hr)	14	58.8	0.1	58.7	58.7, 58.9	13	58.8	0.1	58.7	58.7, 58.9
Fecal Fat Excretion (g/24 hr)	14	**15.9**	2.2	17.8	12.6, 19.3	13	**4.1**	0.5	4.4	0.6, 7.6
Fat excretion (%)	14	**27.1**	3.8	30.3	21.3, 32.8	13	**6.9**	0.8	7.5	1.0, 12.9

4.4 Extrinsic Factors

Not applicable.

4.5 General Biopharmaceutics

Not applicable.

4.6 Analytical

Q. Was the analytical assay for orlistat plasma concentrations adequately validated?

Orlistat and M1 concentrations were determined using a high pressure liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method. The limit of quantitation for the assay was — pg/mL for orlistat and — pg/mL for M1. The precision (%CV) and accuracy of the assay were within the acceptable range of 20%. The precision of the assay, as determined from the analysis of all quality control samples ranged from 1.9 to 6.7% for orlistat and from 1.3 to 3.8% for M1. The accuracy ranged from -1.2 to 1.8 and from -2.9 to 1.1% for orlistat and M1, respectively.

Reviewer's Comments:

The method for determination of M3 concentration was not included in this NDA. The sponsor is recommended to include assay validation for M3 determination in future submission.

5 Comments

The method for determination of M3 concentration was not included in this NDA. The sponsor is recommended to include assay validation for M3 determination in future submission.

6 Labeling

Under CLINICAL PHARMACOLIGY Section Special Populations Subsection:

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 in adolescents 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.

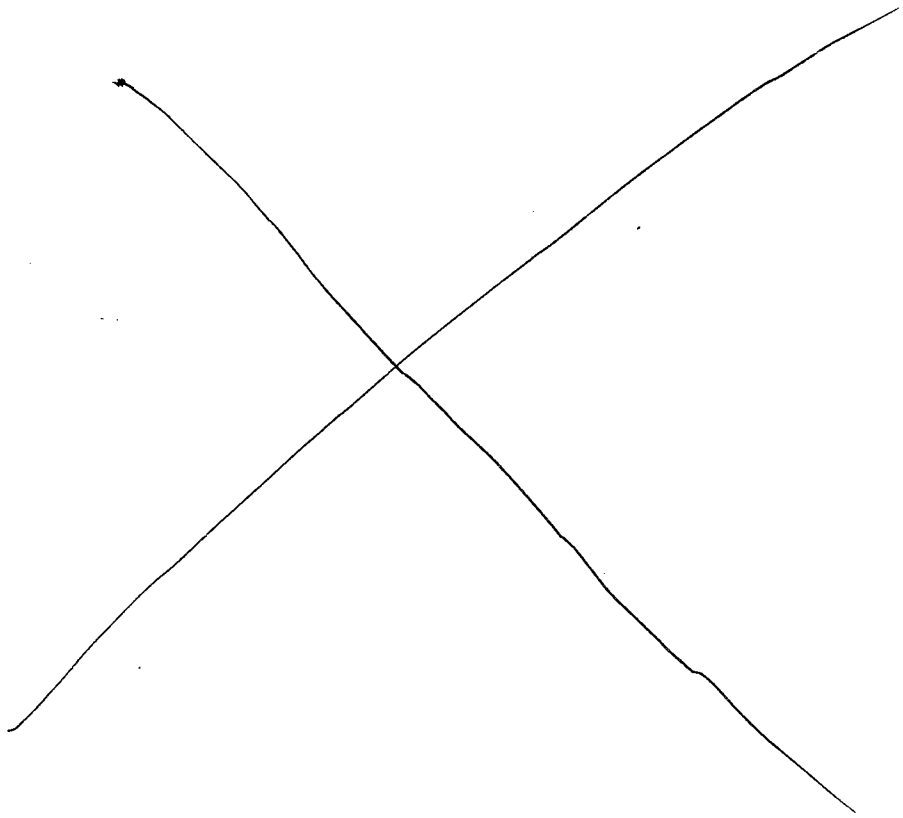
Under CLINICAL PHARMACOLIGY Section Other Short-term Studies

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.

7 Appendix

7.1 proposed labeling



19 Page(s) Withheld

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X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 20-766 SOR

8 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 20-766 S018

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Wei Qiu
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Hae-Young Ahn
12/5/03 09:11:10 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-766/S-018

Administrative/Correspondence

PATENT INFORMATION FOR NDA NO. 20-766

1)	Active Ingredient(s)	Orlistat Tetrahydroplipstatin
2)	Strength(s)	120 mg capsule
3)	Trade Name	Xenical®
4)	Dosage Form and Route of Administration	Capsule Oral
5)	Applicant (Firm) Name	Hoffmann-La Roche Inc.
6)	NDA Number	NDA 20-766
7)	First Approval Date	April 23, 1999
8)	Exclusivity: Date first ANDA could be approved	ANDA can not be approved for at least three (3) years from the date pending NDA is approved
9)	Patent Information	See Attachment

CONFIDENTIAL INFORMATION

*Since the New Drug Application Supplement has not yet been approved, this submission is considered as constituting trade secrets or commercial or financial information which is privileged or confidential within the meaning of the Freedom of Information Act (5 USC 552). It is requested that this submission not be published until the New Drug Application Supplement has been approved.

130822

ATTACHMENT

First US Patent Number: 4,598,089

Expiration Date: June 18, 2009 (includes patent term extension)

Type of Patent-Indicate all that apply (check applicable boxes):

1.	Drug Substance (Active Ingredient)	[X]	Y	[ ]	N
2.	Drug Product (Composition/Formulation)	[X]	Y	[ ]	N
3.	Method of Use	[X]	Y	[ ]	N

If patent claims method(s) of use, please specify approved uses or uses for which approval is being sought that is covered by patent: Method of treating obesity.

Name of Patent Owner: HLR Technology Corporation

US Agent (if patent owner or applicant does not reside or have place of business in the US):

The following declaration statement is required if the above listed patent has Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 4,598,089 covers the composition, formulation and/or method of use of Xenical. This product is:

[X] currently approved under the Federal Food, Drug, and Cosmetic Act.)

OR

[ ] the subject of this application for which approval is being sought.)

Second US Patent Number: 6,004,996

Expiration Date: January 6, 2018

Type of Patent-Indicate all that apply:

1.	Drug Substance (Active Ingredient)	[ ]	Y	[ ]	N
2.	Drug Product (Composition/Formulation)	[X]	Y	[ ]	N
3.	Method of Use	[ ]	Y	[ ]	N

If patent claims method(s) of use, please specify approved uses or uses for which approval is being sought that are covered by patent:

_____.

Name of Patent Owner: Hoffmann-La Roche, Inc.

US Agent (if patent owner or applicant does not reside or have place of business in the US):

The following declaration statement is required if the above listed patent has Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 6,004,996 covers the composition, formulation and/or method of use of Xenical. This product is:

[X] currently approved under the Federal Food, Drug, and Cosmetic Act.)

OR

[ ] the subject of this application for which approval is being sought.)

By: _____
Name: John P. Parise
Date: May 22, 2003
Title: Senior Counsel
Telephone Number: (973) 235-6326

EXCLUSIVITY SUMMARY for NDA # 20-766 SUPPL # -018

Trade Name Xenical Generic Name Orlistat

Applicant Name Hoffmann-La Roche HFD-510

Approval Date December 12, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X_/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

      If yes, what type? SE5

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-766

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # NM16189

Investigation #2, Study # PP16203

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # NM16189

Investigation #__, Study # PP16203

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /_X_/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

/S/

_____

Signature of Preparer Date

Oluchi Elekwachi, Pharm.D., M.P.H.

Title: Regulatory Health Project Manager

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 26, 2003

TO: NDA File

FROM: Kati Johnson, CPMS, HFD-510

SUBJECT: **Pediatric Exclusivity Granted**
NDA 20-766/S-018, Xenical (orlistat) Capsules

A Written Request (WR) was issued for Orlistat on August 9, 2000. An efficacy supplement was submitted in response to this WR on June 23, 2003. The pediatric exclusivity board met on Friday, September 12, 2003 and it was determined that the study conducted for the supplement complied with the terms of the WR. The sponsor of the application was informed of the decision on Monday, September 15, 2003 (contact person at the firm, Encarnacion Suarez, 973-562-5594.

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA 08/09/2000. Application Written Request was made to: NDA# 20-766
Timeframe Noted in Written Request for Submission of Studies 08/01/2003.
NDA# 20-766 Supplement # 018 Choose one: **SE5**
Sponsor Hoffmann-LaRoche, Inc.
Generic Name orlistat Trade Name Xenical Capsules
Strength 120 mg Dosage Form/Route Capsules, oral
Date of Submission of Reports of Studies 06/24/2003.
Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) 09/22/2003.

Was a formal Written Request made for the pediatric studies submitted?	Y ✓	N ___
Were the studies submitted after the Written Request?	Y ✓	N ___
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y ✓	N ___
Was the timeframe noted in the Written Request for submission of studies met?	Y ✓	N ___
If there was a written agreement, were the studies conducted according to the written agreement? OR If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y ✓	N ___
Did the studies fairly respond to the Written Request?	Y ✓	N ___

SIGNED Kate Johnson for E. Colman, MD **DATE** 8/12/03
(Reviewing Medical Officer, Theresa Kehoe, MD) (Team Leader)

Do not enter in DFS - FORWARD TO PEDIATRIC EXCLUSIVITY BOARD, HFD-960.

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity ✓ **Granted** ___ **Denied**

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date
NDA 20-766	4598089	1/15/[illegible]
NDA 20-766	6004996	1/6/[illegible]
NDA 20-766	NCE	4/23/04

SIGNED [signature] **DATE** 9/12/03

Revised: 11/30/2001

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

/s/

Grace Carmouze
9/12/03 03:26:26 PM

Pediatric Exclusivity Determination Template

Written Request Items	Information Submitted/ Sponsor's response
Types of studies/ Study Design: Study 1: A double-blind, placebo-controlled 54-week study (which includes a 2-week lead-in period) of the efficacy and safety of orlistat in the weight management of obese pediatric patients. A multicenter, randomized, double-blind, placebo-controlled, parallel study of obese adolescents. Approximately 450 pediatric patients should be randomized to receive either orlistat or placebo (2:1 randomization) as an adjunct to a hypocaloric diet, following a 2 week placebo lead-in period. All patients should receive nutritional and behavioral modification counseling throughout the study. A multivitamin supplement should be prescribed for all patients. Study 2: A 3-week study of the effect of orlistat on the balance of selected minerals in obese adolescents. An in-patient, double-blind, placebo-controlled, randomized, parallel group, 22 day study. All patients should receive a hypocaloric diet of about 1800kcal, 30% of calories from fat, and maintain a constant mineral content	**Types of studies:** Study 1, NM16189: This was a multicenter, randomized, double-blind, placebo-controlled, parallel study of obese adolescents. Following a 2 week placebo lead-in period, patients were randomized to receive either orlistat or placebo in a 2:1 ratio as an adjunct to a hypocaloric diet for 52 weeks. All patients received nutritional guidance, behavioral modification, and exercise counseling throughout the study. All patients began multivitamin supplementation at the time of randomization. Following the completion of the treatment period, patients were followed for an additional 28 days. Study 2, PP16203: The effect of orlistat on the balance of selected minerals in obese pediatric and adolescent patients. This was an inpatient, single-center, double-blind, randomized, placebo-controlled, parallel-group, in-patient study in obese adolescents where obese was defined as a BMI of $\geq$ 85th percentile adjusted for age and sex at the time of screening.
Indication(s) to be studied: Adolescent obesity.	**Indication(s) studied:** Pediatric Obesity **(Note: The Sponsor uses the term Pediatric, not Adolescent throughout the proposed product label)**
Age group and population in which study will be performed: Study 1 : 12 to 16 years Study 2: 12 to 16 years	**Age group and population in which study was performed:** Study 1 (NM16189): 12 to 16 years at screening **(Note: Five 11 year old patients were enrolled into the study)** Study 2 (PP16203): 12 to 16 years at screening

Number of patients to be studied or power of study to be achieved: Study 1: A total of approximately 450 patients should be enrolled into the study: approximately 300 to orlistat and approximately 150 to placebo. A reasonable distribution of patients in both treatment groups across the age range should be achieved. Each center should be expected to enroll approximately 15 patients. Assuming a 30% drop-out rate, 150 patients per group will provide 80% power at the two-sided 5% alpha level to detect a one BMI unit difference between treatment groups. The standard deviation of change from baseline BMI is estimated at 2.6. Study 2: A total of 24 patients should be randomized in equal fashion to drug or placebo. A reasonable distribution of patients in both treatment groups across the age range should be achieved.	**Number of patients studied or power achieved:** Study 1 (NM16189): A total of 539 patients from 32 study centers were randomized (182 to the placebo group and 357 to the orlistat group). A total of 349 patients completed the study [117 (64%) in the placebo group and 232 (65%) in the orlistat group]. The standard deviation of change from baseline BMI is not larger than the estimated 2.6 and therefore, the power is more than 80%. Study 2 (PP16203): A total of 32 subjects (n = 32) were enrolled in the study and randomized in a 1:1 ratio to either the placebo or orlistat treatment group with an expectation of obtaining 13 evaluable subjects per group. Assuming a standard deviation of 1.75, 80% power, alpha = 0.05 (two-sided test), a difference of 2 mmol/24 hrs in calcium mineral balance could be detected between the two treatment groups. Thirty subjects completed the study.
Written Request Items	**Information Submitted/ Sponsor's response**
Entry criteria: Study 1: Male and female patients who have a body mass index (BMI) at least two units greater than the U.S. weighted mean for the 95th percentile based on age and gender of any racial and ethnic groups will be eligible for study participation. Patients with mild chronic medical conditions such as hypertension, asthma, etc who do not require treatment will be eligible for study participation.	**Entry criteria used:** Study 1 (NM16189): Patients were considered eligible for the study if they met the following criteria: - BMI at the time of screening that was 2 units greater than the US weighted mean for the 95th percentile based on age and gender. - Age: 12 to 16 years at screening - Gender: male or female patients of all racial and ethnic groups. Females of childbearing potential had to have a negative serum pregnancy test at screening and randomization, and had to use an acceptable method of contraception during the study if sexually active.

Exclusion criteria include: - BMI > 44kg/m^2 and or body weight ≥130kg - Body weight < 55 kg - Weight loss ≥ 3 kg within 3 months prior to screening	- Patients without any chronic medical condition or with mild chronic medical conditions (i.e., hypertension, asthma, arthritis, etc.) who do not require treatment or are medically stable on treatment - Availability of a parent or guardian to attend study visits with the patients and to be actively involved in the behavior modification plan. - Give written informed consent before any study specific screening procedures with the understanding that the patient has the right to withdraw from the study at any time. Patients meeting any of the following criteria were excluded from the study: - BMI ≥44 kg/m^2 and/or body weight ≥130 kg - Body weight < 55 kg - Weight loss of ≥ 3 kg within three months prior to screening - Pregnancy or lactation - Diagnoses of diabetes requiring anti-diabetic medication - Obesity associated with genetic disorders such as Prader-Willi, Bardet-Biedl, and Cohen syndromes - History or presence of significant medical (e.g. renal cancer, hepatic cancer, or endocrine disorders) or psychiatric conditions or diseases which could impact on the results of the study, without prior approval of the sponsor - Current use of dexamphetamine or methylphenidate (Ritalin) including in patients diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) - Hypothyroidism not controlled with a stable dose of thyroxine replacement therapy for at least 3 months - Abnormal laboratory test results of clinical significance - Presence of chronic diarrhea or cholestasis, active gastrointestinal disorders such as malabsorption syndrome, ongoing bulimia or laxative abuse - Use of any of the following prohibited medications within 3 months prior to randomization: anorexic medications, prescription and/or over the counter, antidepressants, prescription and/or over the counter, anticonvulsants, antiarrythmic medications, Systemic steroids other than oral contraceptives - Use of approved or experimental weight reduction medications or treatments currently or within 3 months of randomization

Study 2: Healthy male and female patients with a BMI at or above the 85th percentile for age and gender with no major medical or psychiatric conditions.	- Dependence on any substance of abuse, including alcoholism - Unwilling or unable to comply with the protocol requirements or considered by the investigator to be an inappropriate candidate for the study - A known hypersensitivity to orlistat or any of its components - Inability to swallow hard shell ½ capsules - Failure to discontinue the use of all vitamin preparations one month prior to randomization - Participation in a clinical trial within 30 days of screening Study 2 (PP16203): Subjects who met the following criteria were to be included in this study: - BMI ≥ 85th percentile, adjusted for age and sex - Age range: 12-16 years - Gender: male or female - Negative serum pregnancy test at screening and randomization (females of childbearing potential only). Use of an acceptable method of contraception if sexually active - Willingness to give written informed consent and to participate and comply with the study - Non-smoker.
Clinical endpoints: Study 1: The primary endpoint should be change in BMI from baseline to week 54 or study exit. Secondary endpoints should include change in body weight, linear growth, blood pressure, waist circumference, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride levels, insulin and glucose levels at approximately 0 and 120 minutes after orally administered glucose stimulation. Study 2: Primarily, the balance of calcium, copper, iron, magnesium, phosphorus and zinc. Also serum and urine levels of sodium, potassium and creatinine. Fecal fat content on approximately Days 15 and 21.	**Clinical endpoints used:** Study 1 (NM16189): The primary efficacy parameter was change in BMI from baseline to the end of the study. The secondary efficacy parameters were change in body weight, total cholesterol, LDL cholesterol, HDL cholesterol, LDL/HDL ratio, triglycerides, diastolic and systolic blood pressure, waist circumference, and glucose and insulin responses to an oral glucose challenge. In addition, hip circumference and categorical changes in BMI and body weight were analyzed. Study 2 (PP16203): Mineral balance parameters were calculated separately for each subject using the average of the last 7 days (15-22) of treatment. Fecal fat content was measured on Days 15 and 21.

Timing of assessments: Study 1: - Patients should have assessments of Tanner stage at baseline and at approximately Weeks 25 and 54 or study exit. - Serum levels of sex-hormone binding globulin, estradiol (females), and testosterone (males) should be measured at baseline and at approximately Weeks 25 and 54 or study exit. - An electrocardiogram should be taken at baseline and at approximately Week 54 or study exit. - An assessment of changes in body composition should be obtained by DEXA at baseline and at approximately Week 54 or study exit. Study 2: On approximately Days 10 to 22, all urinary and fecal output should be collected. Samples from approximately Days 15 – 22 should be stored for mineral analysis and fecal fat content determination as well as daily urinary creatinine and mineral output.	**Timing of assessments:** Study 1 (NM16189): - Tanner stage was measured at baseline (screening), Week 25 and Week 52 or study end. - Serum levels of sex-hormone binding globulin, estradiol (females), and free testosterone (males) were measured at baseline (Day1), Week 25 and Week 52 or study end. - An electrocardiogram was taken at baseline (Day 1) and Week 52 or study exit. - A subgroup of 18 study centers performed DEXA to assess of changes in body composition baseline and Week 52 or study exit. A total of 229 patients had DEXA assessments (77 in the placebo group and 152 in the orlistat group). Study 2 (PP16203): The total volume of urine voided was collected in 24-hour intervals (7 am to 7 am of the following day) starting in the morning of day 10 through day 22. On the morning of days 1 and 22, a urine sample (10 mL) was collected from fasted subjects for the determination of sodium and potassium. On study days 15 through 22, a 50 mL aliquot for analysis of calcium, copper, iron, magnesium, phosphorous, and zinc was collected. Fecal collection commenced on the morning of day 10 and continued through to the morning of day 22. Samples collected on days 15 to 22 were analyzed for mineral output and for fecal fat content.
Drug specific safety concerns: The primary safety concerns are the effects of treatment with orlistat on serum levels of fat-soluble vitamins, linear growth, bone mineral content, and the risk of renal calculi and gallstones. Appropriate measures should be taken to monitor and assess these safety issues. An additional safety concern is the effect of orlistat	**Drug specific safety concerns evaluated:** Study 1 (NM16189): Safety parameters included adverse events, laboratory tests, pulse rate, 12-lead ECG, physical examinations, linear growth, Tanner stage assessment, bone mineral content, body composition, fat soluble vitamin and beta-carotene levels, and gallbladder and renal ultrasound findings.

on serum levels of various minerals. This will be addressed in a separate mineral balance study.	Study 2 (PP16203): Safety assessments included adverse events, clinical laboratory parameters, vital signs, and 12-lead electrocardiograms (ECGs).
Drug information (Studies 1 and 2): • **Route of administration: oral** • **Dosage: capsules** • **Regimen: 120mg or placebo three times per day with meals** • **Formulation: same as marketed**	**Drug information:** • **Route of administration: oral** • **Dosage: capsules** • **Regimen: 120mg or placebo three times per day with meals. Patients in study PP16203 also received one capsule containing 10 radio-opaque markers three times a day with meals.** • **Formulation: same as marketed**
Statistical information (statistical analyses of the data to be performed): Study 1: All randomized patients who receive at least one dose of study medication and have a safety follow-up visit will be included in the safety analysis population. All randomized patients who receive at least one dose of study medication and have a follow-up visit for BMI will be included in the primary efficacy analysis. Study 2: The pharmacodynamic parameters should be assessed for all patients who complete the study. Mineral balance data from approximately the last 7 days of treatment will be used for between-treatment comparisons. The 95% confidence interval will be used to estimate the difference between orlistat and placebo groups	**Statistical information (statistical analyses of the data to be performed):** Study 1 (NM16189): Efficacy was analyzed for all patients who had baseline efficacy assessments and at least one post-baseline efficacy measurement (ITT population). Primary and secondary efficacy endpoints were also analyzed for all patients who completed a final visit at week 52 (Completers population). All efficacy endpoints were derived using the last-observation-carried-forward (LOCF) data set. Change from baseline to week 52 in BMI was analyzed using an analysis of covariance model (ANCOVA) that included change from baseline value as the response, and treatment, center, and treatment-by-center, and baseline stratification terms. Study 2 (PP16203): Subjects who completed the study were included in analyses of electrolytes and urine creatinine. Non-completers (Subjects 0015 and 0033) were excluded. **It was necessary to redefine the analysis population used for analyses of mineral balance and fecal fat since 3 subjects did not have fecal samples during the day 15 to day 22 collection period. This population included subjects who completed the study and had at least one recovered**

	fecal maker during the day 15 to day 22 collection period. This analysis population includes 14 orlistat-treated subjects and 13 placebo-treated subjects. Two non-completers (placebo, Subject 0015; orlistat, Subject 0033) were excluded, as were 3 subjects (placebo, Subjects 0010 and 0040; orlistat, Subject 0003) who had no fecal marker recovery during the day 15 to day 22 collection period. Mean fecal marker recovery for this population was 70% for the placebo treatment group and 69% for the orlistat treatment group. The analysis population was redefined to include the pharmacokinetic measurements from one orlistat-treated subject who withdrew on Day 17. For this subject, all measurable concentrations up to and including Day 14 were used in the analyses.
Labeling that may result from the studies: Appropriate sections of the label may be changed to incorporate the findings of the studies.	**Did the sponsor submit proposed labeling?** The sponsor proposes no changes to the indications and usage section of the product label. The Sponsor does propose labeling changes under the pharmacokinetic section, adding a pediatric subsection. The sponsor also proposes adding information regarding this trial to the Clinical Studies section labeled as a Pediatric Clinical Studies subsection.
Format of reports to be submitted: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment and interpretation.	**Format of reports submitted:** Full study reports of studies NM16189 and PP16203 were submitted in electronic format, with full analysis, assessment and interpretation.
Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before August 1, 2003.	**Date study reports were submitted:** Reports of the studies were submitted on June 24, 2003.
Additional Information:	

DEBARMENT CERTIFICATION

Hoffmann-La Roche Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: June 30, 2002

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☑ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	SEE ATTACHMENT	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Cynthia Dinella, Pharm.D.	**Vice President, Drug Regulatory Affairs**
FIRM/ORGANIZATION **Hoffmann-La Roche Inc.** **340 Kingsland Street** **Nutley, New Jersey 07110**	
SIGNATURE	DATE **May 22, 2003**

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

10 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 20-766
5018

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NO FILING ISSUES IDENTIFIED

NDA 20-766/S-018

Hoffmann-La Roche, Inc.
Attention: Encarnacion Suarez, PharmD
Senior Program Manager, Drug Regulatory Affairs
340 Kingsland Street
Nutley, New Jersey 07110-1199

8/11/03

Dear Dr. Suarez:

Please refer to your June 23, 2003 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xenical (orlistat) Capsules.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on August 23, 2003 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

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

Sincerely,

{See appended electronic signature page}

Kati Johnson
Chief, Project Management Staff
Division of Metabolic & Endocrine Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ACK 7/3/03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-766/S-018

Hoffmann-La Roche, Inc.
Attn: Encarnacion Suarez, Pharm.D.
Senior Program Manager, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Dr. Suarez:

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
NDA Number:	20-766
Supplement number:	S-018
Review Priority Class:	Priority (P)
Date of supplement:	June 23, 2003
Date of receipt:	June 24, 2003

This supplemental application responds to a pediatric Written Request and provides revised labeling to provide for the use of Xenical in obesity management of adolescent patients aged 12 to 16 years. Your submission also requests a determination of pediatric exclusivity.

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 August 23, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be December 24, 2003.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6380.

Sincerely,

/s/

{See appended electronic signature page}

Kati Johnson
Chief, Regulatory Project Management Staff
Division of Metabolic & Endocrine Drug Products
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/

Enid Galliers
7/3/03 12:31:47 PM
Signing for Ms. Johnson

HFD-104
VHA0

NDA 20-766

AUG 9 2000

Hoffmann-La Roche Inc.
Attention: Margaret J. Jack
Program Director
340 Kingsland St.
Nutley, NJ 07110-1199

Dear Ms. Jack:

Reference is made to your proposed Pediatric Study Request for Xenical (orlistat) Capsules submitted on March 17, 2000 to NDA 20-766.

We also acknowledge your amendment dated April 7, 2000.

To obtain needed pediatric information on orlistat, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

Study #1

Type of Study:

A double-blind, placebo-controlled, 54-week study (which includes a 2-week lead-in period) of the efficacy and safety of orlistat in the weight management of obese pediatric patients.

Objectives:

To characterize the efficacy of orlistat as an adjunct to diet in the treatment of obesity in pediatric patients. To characterize the safety profile of orlistat in obese pediatric patients, including:

-Gastrointestinal tolerability
-Linear growth and Tanner pubertal stage assessment
-Bone mineral content and body composition measured by DEXA
-Fat-soluble vitamins, beta-carotene, PTH, and serum calcium levels
-Gall bladder and renal ultrasound

Indication to be studied:

Adolescent obesity

Study design:

A multicenter, randomized, double-blind, placebo-controlled, parallel study of obese adolescents. Approximately 450 pediatric patients should be randomized to receive either orlistat or placebo (2:1 randomization) as an adjunct to a hypocaloric diet, following a 2-week placebo lead-in period. All patients should receive nutritional and behavior modification counseling throughout the study. A multivitamin supplement should be prescribed for all patients.

Age group in which studies will be performed:

Ages 12 to 16 years.

Number of patients to be studied:

A total of approximately 450 patients should be enrolled into the study: approximately 300 to orlistat and approximately 150 to placebo. A reasonable distribution of patients in both treatment groups across the age range should be achieved. Each center should be expected to enroll approximately 15 patients.

Entry criteria:

Male and female patients who have a body mass index (BMI) at least two units greater than the U.S. weighted mean for the 95th percentile based on age and gender of any racial and ethnic groups will be eligible for study participation. Patients with mild chronic medical conditions such as hypertension, asthma, etc. who do not require treatment will be eligible for study participation. Exclusion criteria include:

-BMI > 44 kg/m^2 and/or body weight $\geq$ 130 kg
-body weight < 55 kg
-weight loss $\geq$ 3 kg within 3 months prior to screening

Clinical endpoints:

The primary endpoint should be change in BMI from baseline to Week 54 or study exit. Secondary endpoints should include change in body weight, linear growth, blood pressure, waist circumference, total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride levels, insulin and glucose levels at approximately 0 and 120 minutes after orally administered glucose stimulation.

Study evaluations:

Patients should have assessments of Tanner stage at baseline and at approximately Weeks 25 and 54 or study exit. Serum levels of sex-hormone-binding globulin, estradiol (females), and testosterone (males) should be measured at baseline and at approximately Weeks 25 and 54 or study exit. An electrocardiogram should be taken at baseline and at approximately Week 54 or

study exit. An assessment of changes in body composition should be obtained using DEXA at baseline and at approximately Week 54 or study exit.

Drug information:

- Dosage form: capsules
- Route of administration: oral
- Regimen: 120 mg or placebo three times per day with meals
- Formulation: same as marketed

Drug specific safety concerns:

The primary safety concerns are the effects of treatment with orlistat on serum levels of fat-soluble vitamins, linear growth, bone mineral content, and the risk for renal calculi and gallstones. Appropriate measures should be taken to monitor and assess these safety issues. An additional safety concern is the effect of orlistat on serum levels of various minerals. This will be addressed in a separate mineral balance study (see below).

Statistical information:

Assuming a 30% drop-out rate, 150 patients per group will provide 80% power at the two-sided 5% alpha level to detect a one BMI unit difference between treatment groups. The standard deviation of change from baseline BMI is estimated at 2.6. To provide additional safety information, approximately 300 patients should be randomized to the orlistat arm while approximately 150 patients should be randomized to the placebo arm.

All randomized patients who receive at least one dose of study medication and have a safety follow-up visit will be included in the safety analysis population. All randomized patients who receive at least one dose of study medication and have a follow-up visit for BMI will be included in the primary efficacy analysis.

Study #2

Type of study:

A 3-week study of the effect of orlistat on the balance of selected minerals in obese adolescents.

Objectives:

To assess the effect of orlistat (120 mg three times per day) on the balance of selected minerals in obese pediatric patients; to assess the effect of orlistat on plasma and urine electrolyte levels; and to evaluate the effect of orlistat on the extent of fat excretion.

Indication to be studied:

Not applicable.

Study design:

An in-patient, double-blind, placebo-controlled, randomized, parallel-group, 22-day study. All patients should receive a hypocaloric diet of about 1800 kcal, 30% of calories from fat, and maintain a constant daily mineral content.

Age group in which study will be performed:

Ages 12 to 16 years.

Number of patients to be studied:

A total of approximately 24 patients should be randomized in equal fashion to drug or placebo. A reasonable distribution of patients in both treatment groups across the age range should be achieved.

Entry criteria:

Healthy male and female patients with a BMI at or above the 85th percentile for age and gender with no major medical or psychiatric conditions.

Clinical endpoints:

Primarily, the balance of calcium, copper, iron, magnesium, phosphorus, and zinc. Also, serum and urine levels of sodium, potassium, and creatinine. Fecal fat content on approximately Days 15 and 21.

Study evaluations:

On approximately Days 10 to 22, all urinary and fecal output should be collected. Samples from approximately Days 15-22 should be stored for mineral analysis and fecal fat content determination as well as daily urinary creatinine and mineral output.

Drug information:

- **Dosage form:** capsules
- **Route of administration:** oral
- **Regimen:** 120 mg three times per day with meals
- **Formulation:** same as marketed

Drug specific safety concerns:

See *Study evaluations.*

Statistical information:

The pharmacodynamic parameters should be assessed for all patients who complete the study. Mineral balance data from approximately the last 7 days of treatment will be used for between-treatment comparisons. The 95% confidence interval will be used to estimate the difference between orlistat and placebo groups.

Labeling that may result from these studies:

Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of reports to be submitted: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.

Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before August 1, 2003. Please remember that pediatric exclusivity extends only existing patent protection or exclusivity that has not expired or been previously extended at the time you submit your reports of studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of

the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Maureen Hess, MPH, RD, Regulatory Health Project Manager, at (301) 827-6411.

Sincerely yours,

John K. Jenkins, MD
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Cc:
NDA 20-766
IND 31,617
HFD-510
/MHess/EColman/MHaber/DWu/DHertig/JElHage/HAhn/SMadani/LPian/TSahlroot
HFD-102/JJenkins/LRipper
HFD-600/Office of Generic Drugs
HFD-2/MLumpkin
HFD-104/Peds/DMurphy
HFD-104/Peds/TCrescenzi/VKao

Drafted by: MHess/5.11.00
Initialed by:
LPian/6.5.00/TSahlroot/6.6.00/SMadani/5.23.00/HAhn/6.1.00/EColman/6.5.00/EGalliers/6.7.00/
LRipper/6.8.00 and 7.31.00/JJenkins/6.23.00 and 8.2.00
PDIT: 7.26.00 and 8.8.00
Final: 8.8.00

PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)

510/Alees

IC
510

NDA 20-766

OCT 6 1999

Hoffmann-La Roche Inc.
Attention: Margaret J. Jack
Program Director
Drug Regulatory Affairs
340 Kingsland St.
Nutley, NJ 07110-1199

Dear Ms. Jack:

Reference is made to your correspondence dated August 18, 1999, requesting FDA to issue a Written Request under Section 505A of the Food, Drug, and Cosmetic Act for orlistat.

We have reviewed your proposed pediatric study request and are unable to issue a Written Request based on your submission.

We recommend you resubmit your proposed pediatric study request addressing all of the issues outlined below.

1. A one-year study of efficacy and safety in obese adolescents between the ages of 12 and 16.
2. A placebo-controlled study that includes a total of 300 subjects randomized to orlistat treatment.
3. Effect of the drug on fat-soluble vitamin and beta-carotene levels.
4. Effect of the drug on bone density and linear growth.
5. Effect of the drug on mineral balance.
6. Effect of the drug on body composition.
7. Estimates of the racial mix of the study.
8. Estimates of the gender mix of the study.
9. Effect of the drug on risk for renal and gallstones.

Please clearly mark your submission, "PROPOSED PEDIATRIC STUDY REQEUST" in large font, bolded type at the beginning of the cover letter of the submission.

We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, contact Maureen Hess, MPH, RD, Regulatory Health Project Manager, at (301) 827-6411.

Sincerely yours,

/S/ 10/6/99

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Cc:
NDA 20-766
HFD-510/Div. File
HFD-510/EColman/GTroendle/MHess
HFD-102/JJenkins
HFD-2/MLumpkin
HFD-104/DMurphy
HFD-002/TCrescenzi

Drafted by: MHess/9.29.99
Initialed by: EColman/9.29.99/GTroendle/9.29.99/EGalliers/10.1.99/
Final: 10.5.99

INADEQUATE PEDIATRIC STUDY REQUEST
INFORMATION REQUEST (IR)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Encarnacion Suarez, Pharm.D.
Hoffmann-La Roche Inc.
340 Kingsland Avenue
Nutley, New Jersey 07110-1199

2. TELEPHONE NUMBER *(Include Area Code)*

(973) 562-5594

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 20-766

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

3. PRODUCT NAME

Xenical® (orlistat, Ro 18-0647) Capsules

6. USER FEE I.D. NUMBER

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?

☐ YES ☒ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
E. Suarez	Encarnacion Suarez, Pharm.D. Senior Program Manager	5/29/2003

FORM FDA 3397 (1/00)