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:

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).

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 0.20 to 10.90 ng/mL, while historical data showed that at the same dose level, measurable orlistat

concentration ranging from 0.21 to 8.3 ng/mL were found in 40 to 60% adult patients. Plasma concentrations of M1 and M3 were 20.15 and 70.39 ng/mL at day 141, 14.49 and 66.00 n/mL 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 0.428 ng/mL, 32.7 ng/mL, and 117.2 ng/mL, 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 0.20 to 10.90 ng/mL. 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 (0.20-10.90)	37.2	20.15 (174)	43.22	70.39 (169)	59.35
337	156	46 (0.21-7.42)	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 0.20 to 10.90 ng/mL. 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 0.21 to 8.3 ng/mL 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 (0.21-4.66)	38	21.6 (94)	14.5	68.9 (91)	41.4
5	118	76 (0.21-8.3)	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 subtracting fecal and urinary mineral content from dietary mineral intake. Fecal mineral content was normalized by dividing raw fecal mineral content by the ratio of the actural number of radio-opaque markers counted in fecal samples to the expected number excreted.

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 200 pg/mL for orlistat and 320 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.

(b) (4)

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

27 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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