EFFICACY RESULTS:

After one year of treatment with 120 mg tid of orlistat, patients lost an average of 6.2% of initial body weight compared with 4.3% for placebo-treated patients. The least squares mean (LSM) difference from placebo-treated patients in weight loss was statistically significant ($p<0.05$; 2.4 kg difference). Forty-nine percent of orlistat-treated patients, but only 23% of placebo-treated patients lost more than 5% of their initial body weight in the ITT population. Conversely, 20% of placebo-treated patients gained up to 5% of their initial body weight by the end of one year, while only 6% of orlistat-treated patients did so.

After 52 weeks of double-blind treatment, the mean change in dose of oral hypoglycemic agent (OHA) was -23% for the orlistat-treated group and -9% for the placebo-treated group. The least squares mean change in dose of OHA for the ITT Population after 52 weeks was significantly different ($p=0.0019$) between the two treatment groups. Over the 52 weeks of double-blind treatment, the mean change from baseline fasting blood glucose levels was 0.7% for the orlistat-treated group, while the placebo-treated group had increased by 8.2%. The difference in the least squares mean change in fasting blood glucose levels between orlistat and placebo groups was statistically significant ($p<0.05$) after 52 weeks of treatment. The orlistat-treated group had a mean decrease in hemoglobin A1c of 0.2%, while the placebo-treated group had a small increase of 0.3% at the end of 52 weeks of double-blind treatment. The difference in the least squares mean between the placebo- and orlistat-treated groups was statistically significant ($p\leq 0.016$; 0.45% difference) for all of the analysis populations.

There was a small reduction in the mean diastolic blood pressure (less than 1 mm Hg) in both treatment groups during the 52 week double-blind treatment period. The difference in the least squares mean change in fasting insulin levels between the orlistat and placebo groups was not statistically significant after 52 weeks of treatment. There were statistically significant decreases ($p\leq 0.04$) in the orlistat-treated group compared with the placebo-treated group in the least squares mean levels of total cholesterol, LDL-cholesterol, triglycerides, LDL/HDL ratio and apolipoprotein B after 52 weeks of treatment. The mean change in the waist circumference, after 52 weeks of double-blind treatment was -2.0 cm in the placebo-treated group and 4.8 cm in the orlistat-treated group. There were small or no improvement in the Quality of Life outcome measures of health distress and depression. Both groups had a decline in satisfaction with treatment, however at week 52, the decline in the orlistat group was statistically significantly less than the placebo group ($p=0.000$).

SAFETY RESULTS:

Adverse events were mild to moderate in intensity in both treatment groups. The majority of adverse events were judged by the investigators to be unrelated or remotely related to treatment. In the orlistat-treated group, there were more adverse events which were judged to be probably related to treatment. The larger number of adverse events in the orlistat group is likely due to the larger number of known orlistat effects occurring in this group. A total of 58.5% of placebo- and 79.0% of orlistat-treated patients had GI adverse events. The difference in the incidence of GI adverse events is related to the pharmacological effect of orlistat which included fatty/oily stool (0% of placebo patients, 19.8% of orlistat patients), liquid stools (9.4% of placebo patients and 16% of orlistat patients), oily evacuation (0% placebo patients and 14.2% of orlistat patients), increased defecation (3.1% of placebo patients and 11.1% of orlistat patients), fecal urgency (5.7% of placebo patients and 29.6% of orlistat patients), oily spotting (1.9% of placebo patients and 32.7% of orlistat patients), flatus with discharge (1.9% of placebo patients and 40.1% of orlistat patients), fecal incontinence (1.3% of placebo and 11.7% of orlistat patients) and flatulence (13.2% of placebo and 23.5% of orlistat patients). The majority of patients in both treatment groups had only one or two episodes of the GI adverse events.

Serious adverse events were uncommon during the study. Fifteen placebo–treated patients had at least one serious adverse event, 13 of whom had events considered by the investigator to be unrelated to treatment. Eleven orlistat–treated patients had at least one serious event, all of which were considered by the investigator to be unrelated to treatment. Only one placebo– and one orlistat–treated patient had gastrointestinal adverse events which met the criteria for being considered serious. Twenty–three placebo– and twelve orlistat–treated patients withdrew prematurely from the study because of adverse events. Seven orlistat–treated patients and two placebo–treated patients terminated because of GI adverse events; all were thought to be either probably or possibly related to orlistat treatment. Fifteen placebo– and five orlistat–treated patients withdrew prematurely because of hyperglycemia.

There were no clinically significant changes in the mean values of any of the standard laboratory parameters over the course of the double–blind treatment period in either treatment group. The most common marked laboratory abnormalities in both treatment groups were elevated prothrombin time i.n.r., high WBC in urine and high glucose in urine. Eighty–six percent of orlistat patients and 89% of placebo patients who had normal ECG results at the start of double–blind treatment also had normal results at the end of double–blind treatment. Of 80 orlistat patients who had normal ECG results at baseline, 11 had abnormalities at the end of treatment. Of 69 orlistat–treated patients who had abnormal ECG results at the start of double–blind treatment 14 patients developed a new abnormality at the end of treatment. The decrease (difference in LSM change from placebo) in vitamin levels after 52 weeks of treatment with orlistat was statistically significant (p=0.000) for vitamin E and beta–carotene although the mean values remained within normal limits. There was no significant change noted in the vitamin E/cholesterol ratio in either treatment group. New abnormalities in gallbladder ultrasound results were detected at the end of the study in 14% of orlistat– and 24% of placebo–treated patients.

PHARMACODYNAMIC RESULTS:

After 52 weeks of treatment, mean fecal fat excretion was increased by 25 g/day in orlistat–treated patients. There was no change in fecal fat excretion among placebo–treated patients.

PHARMACOKINETIC RESULTS:

Minute quantities of orlistat (range of 0.21 to 8.3 ng/mL) were detectable in the plasma of approximately two–thirds of the samples from orlistat–treated patients after 20 weeks of treatment. Plasma concentrations of M1 metabolite and M3 metabolite appeared to be much higher than plasma concentrations of unchanged orlistat.

CONCLUSIONS:

The results of this study indicate that obese patients with NIDDM maintained on a hypocaloric diet lost significantly more weight when treated with 120 mg of orlistat tid for 52 weeks than when treated with placebo tid for 52 weeks. This enhanced weight loss was associated with significant improvement in the patients' glycemic control. Orlistat was well tolerated when administered to obese NIDDM patients at a dose of 120 mg tid for 52 weeks.

Reviewer's Comments: Assay sufficiently validated. [redacted]

[redacted]
APPEARS THIS WAY ON ORIGINAL

Summary of plasma orlistat, M1, and M3 pharmacokinetics for protocol NM14336

Variable	Placebo	Orlistat (120 mg)			
	N/Total	N/Total	Mean	Range	CV (%)
Analyte[a]					
orlistat	3/113[b]	76/118	1.48	0.21 - 8.3	113
M1	2/113[c]	115/118	31.4	3.0 - 120.6	70
M3	NA	101/101	107	16 - 353	66
Ratio					
M1/orlistat		76	50.0	5.3 - 165.2	77
M1/M3		101	0.34	0.05 - 1.27	63

NA: Not Assayed

N/Total = No. of samples containing measurable concentrations/total no. of samples.

[a] The unit of plasma concentrations is ng/mL.

[b] Reported concentrations were: 0.3, 0.26, and 0.23 ng/mL.

[c] Reported concentrations were: 0.32 and 0.52 ng/mL.

APPEARS THIS WAY ON ORIGINAL

Appendix 1.3. Mass Balance

Appendix 1.3.1. Excretion Balance And Pharmacokinetic Study with [redacted]C-Labeled Tetrahydrolipstatin (THL, Ro 18-0647/004) after a Single Oral Dose in Healthy Volunteers (Protocol P-7166)

STUDY NO.: VOLUME: PAGES:

OBJECTIVES:
To determine plasma concentrations, routes of elimination and excretion balance of total radioactivity after a single oral dose of Ro 18-0647/004 in healthy volunteers.

INVESTIGATOR/SITE:
[redacted]

FORMULATIONS:
Capsules (Ro 18-0647/046, batch no. GMZ 743 A01) with 50 mg Ro 18-0647/004

STUDY METHODS:
(a) Design: Open single group study with a single oral dose of 50 mg of ^{14}C -labeled Ro 18-0647/004 (50μCi).

(b) Demographics:

Gender (M/F)	Age (yr)	Weight (kg)	Origin
6/0	18 - 34	54 - 86	--

(c) Sampling times:

Blood: 0 h (predose); and 0.25, 0.5, 1, 2, 4, 8, 12, 48, 56, 72, 80, 96, 104, and 120 h postdose

Urine: 0 h (predose); and 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-32, 32-48, 48-56, 56-72, 72-80, 80-96, 96-104, 104-120, 120-144 h postdose

Feces: Day -1, 0, 1, 2, 3, 4, 5, 6

ASSAY:
Whole blood, plasma, urine, and fecal radioactivity was measured by liquid scintillation counting; unchanged Ro 18-0647 in plasma and urine was determined by a [redacted] method following a specific cleanup.

DATA ANALYSIS:
Descriptive statistics of observed parameters (urinary excretion, fecal excretion, and plasma concentration of total radioactivity).

CONCLUSION/LABELING CLAIM:
Within 5 days after oral administration of [redacted]C-labeled THL, excretion of radioactivity in urine (4.1%) and feces (100%) amounted to about 100% of the dose.

Reviewer's Comments: 1) [redacted]assay used external standard method and oxidizer, but no validation data or description of validation procedures submitted. All orlistat plasma concentrations < LOQ (5ng/mL) using [redacted]
2) Low dose/radioactivity in this study; other radiolabeled studies used higher dose/radioactivity and provided better validation data/description.
3) not TBM formulation.
4) This study is of qualitative use only.
[redacted]

Appendix 1.3.2. Pharmacokinetics Of [redacted]C-Labeled Orlistat (Ro 18-0647) in Healthy Volunteers (Protocol NK14178A)

OBJECTIVES:

1. To determine the pharmacokinetics and metabolism of ^{14}C-labeled orlistat in healthy male volunteers.
2. To establish the metabolite patterns of oral orlistat in the plasma and urine samples.
3. To assess the mass balance relationship between the dose of radioactivity orally administered and that eliminated from the body.

INVESTIGATOR/SITE:

[redacted]

FORMULATIONS:

Orlistat: 120-mg capsules each containing approximately 67 μCi (Ro 18-0647/004, lot no. PR 8797-178-1) clinical order no. C171562-01

STUDY METHODS:

(a) Design: Open-label study with a single oral dose of 360 mg of [redacted]C-labeled Ro 18-0647/004 (~ 200 μCi).

(b) Demographics:

Gender (M/F)	Age (yr)	Weight (kg)	Origin
8/0	28 - 39	63.0 - 104.0	3 White/3 Black/ 2 Hispanic

(c) Sampling times:

Plasma: 0 h (predose); and 2, 4, 6, 8, 12, 18, 24, 36, 48, and 72 h postdose.
Urine: -12-0 h (predose); and 0-4, 4-8, 8-12, 12-24, 24-48, and 48-72 h postdose.
Feces: Day -1 and at daily intervals for five days (120 h) postdose.

ASSAY:

Plasma, urine and fecal radioactivity was measured by liquid scintillation counting.
Plasma concentrations of unchanged orlistat were determined using the [redacted] method.
Fecal amount of unchanged orlistat was determined by a not-yet validated assay procedure.

DATA ANALYSIS:

Descriptive statistics of observed PK parameters (urinary excretion, fecal excretion, and plasma concentration of total radioactivity). Due to limited sample volume, the metabolic pattern was not characterized, and, thus, the second objective of the study was not achieved.

CONCLUSION/LABELING CLAIM:

After an oral dosing with orlistat, almost the entire dose was recovered from fecal samples; 83% was unchanged orlistat. Urinary excretion was less than 2%. Within 5 days after oral administration, > 95% of the dose was excreted.

Reviewer's Comments: 1) Scintillation assay used external standard method with standards supplied by scintillation counter vendor, but validation data not submitted (As per John Strong: Details of oxidizer performance checks are not included. It appears that no ^{14}C-labeled spiked feces samples were used to establish calibration curves over the range of analysis.). All orlistat plasma concentrations were < LOQ (5ng/mL) using [redacted] but no validation data were submitted.
2) not TBM formulation.
[redacted]

Appendix 1.3.3. The Metabolic Profile Of [redacted]C-Labeled Orlistat (Ro 18-0647) in Obese Volunteers (Protocol NK14883B)

OBJECTIVES:
To determine the metabolic profile of ^{14}C-labeled orlistat in the plasma and urine of obese volunteers.

INVESTIGATOR/SITE:
[redacted]

FORMULATIONS:
Orlistat: 120-mg capsules each containing ~122 μCi of [redacted]C-labeled orlistat (Ro 18-0647/004, lot #12306-131-1) clinical order no. C181424

STUDY METHODS:
(a) Design: Open-label study with a single oral dose of 360 mg of Ro 18-0647/004 (~ 400 μCi).

(b) Demographics:

Gender (M/F)	Age (yr)	Weight (kg)	Origin
5/3	23 - 68	83.0 - 103.0	7 White/ 1 Hispanic

(c) Sampling times:
Plasma: 4, 6, 8, and 10 h postdose.
Urine: 0-8, 8-12, and 12-24 h postdose.
Feces: Daily intervals until discharge.

ASSAY:
Plasma, urine and fecal radioactivity was measured by liquid scintillation counting. Plasma concentrations of unchanged orlistat and metabolites Ro 42-3988 (M1), Ro 42-2556 (M3), and Ro 61-0591 (M9) were analyzed by [redacted].

DATA ANALYSIS:
Descriptive statistics of observed PK parameters (urinary excretion, fecal excretion, and plasma concentration of total radioactivity).

CONCLUSION/LABELING CLAIM:
The disposition of orlistat appears to be similar between normal and obese subjects. Of the ~ 3% of the dose that is absorbed systemically as inactive metabolites, the presence of two major species (M1 and M3) accounts for ~ 42% of the total radioactivity in plasma. The primary metabolite (M1) has a short disappearance half-life (~ 2 h) whereas that for the secondary metabolite (M3) was slightly longer.

Reviewer's Comments: 1) Scintillation assay used external standard method with standards supplied by [redacted] vendor; validation data submitted. Orlistat/metabolite plasma concentrations measured with validated [redacted] Oxidizer efficiency was checked with manufacturer-supplied standards. (As per John Strong: Details of oxidizer performance checks are not included. It appears that no [redacted]C-labeled spiked feces samples were used to establish calibration curves over the range of analysis. The sponsor submitted this reply: "We typically do not fortify control tissue homogenate with a known amount of labeled test sustance. The quantitation is achieved via ... two calibrations (determination of oxidation efficiency of the sample oxidizer and validation of the liquid scintillation counter quench curve). not by some type of linear calibration curve established by some number of standards of known concentration (as is the case for chromatographically-based analysis).")
2) not TBM formulation.
[redacted]

Appendix I.4. Synopsis of Research Report N–138712 (Protocol ND14278)

COMPANY: Hoffmann–La Roche Inc. NAME OF FINISHED PRODUCT: NAME OF ACTIVE INGREDIENT:	INDIVIDUAL STUDY TABLE REFERRING TO PART ... OF THE DOSSIER: Volume: ..... Page:	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY/REPORT NO./ DATE OF REPORT	Olistat NDA Summary: Human Phamacokinetics and Bioavailability. Research Report N–138712 / July 31, 1996.
INVESTIGATOR(S) / CENTER(S)	[redacted]
PUBLICATION	None
PERIOD OF TRIAL	09 Sept 94 – 20 Sept 95
OBJECTIVES	To evaluate if a 4–week treatment of Xenical™ (Orlistat) in addition to a hypocaloric diet increases cholesterol saturation of gallbladder bile or decreases gallbladder motility compared with diet alone.
STUDY DESIGN	Double–blind, randomized, placebo–controlled, parallel-group, outpatient study.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Obese subjects, body mass index 30 to 43

NUMBER OF SUBJECTS

Enrolled	Evaluable				Discontinued	
	PD	PK	Safety	AEs	Death	Other Reason
23	23	23	23	0	0	0

DEMOGRAPHIC DATA

	PLACEBO	ORLISTAT
Sex (M/F)	6/6	5/6
Age (yr) Mean	39.8	40.2
Weight (kg) mean	98.9	103.6
BMI (kg/m^2) mean	33.3	35.7

TRIAL DRUG / STROKE (BATCH) NOs DOSE / ROUTE / REGIMEN / DURATION	Ro 18–0647 (orlistat)/C176183 (PT2157T38) 120 mg/p.o./t.i.d./28 days
REFERENCE DRUG / STROKE (BATCH) NOs DOSE / ROUTE / REGIMEN / DURATION	Matching placebo for orlistat/C175063 (PT 2160T31) 1 capsule/p.o./tid./28 days

PROCEDURES

Subjects who met the inclusion criteria, underwent baseline determinations of gallbladder motility and gallbladder bile composition. Subjects were randomized to receive 120 mg of Xenical™ (orlistat) or matching placebo to be taken with the three main meals (breakfast, lunch, and dinner) for 28 days. The subjects were placed on a nutritionally balanced weight loss diet for 28 days as outpatients. Gallbladder motility was reassessed on day 28. On day 29, after an overnight fast, an ultrasound of the gallbladder was obtained and the gallbladder bile sampling and analysis was repeated. Laboratory tests for safety evaluations and vital signs were performed during the screening period, at baseline and after study completion (day 29). Clinical adverse events were continuously monitored during the study.

PHARMACODYNAMICS RESULTS:

There were no differences from baseline between treatment groups with regards to cholesterol saturation of bile or gallbladder motility. Phospholipid concentrations tended to decrease in both groups, reaching statistical significance in the placebo group. Total bile acid levels also decreased significantly in the placebo group but were not markedly changed in the orlistat group. The concentration and percent distribution of bile acids in bile were unchanged during orlistat treatment but decreased during placebo treatment.

PHARMACOKINETIC RESULTS:

Bile samples collected before and after 4 weeks of treatment were analyzed for the presence of unchanged orlistat and its primary metabolite, M1 (Ro 42-3988). Orlistat was detected in the bile of all but two orlistat-treated subjects and the M1 was detected in all but three orlistat-treated subjects. Bile concentrations of orlistat and M1 ranged from <2 to 43.5 ng/mL and <2 to 46.2 ng/mL, respectively. The average ratio of M1 to orlistat in the bile was close to unity.

SAFETY RESULTS:

Nineteen adverse events were reported by eleven subjects who received orlistat and five adverse events were reported by three subjects who received placebo. Most adverse experiences were gastrointestinal disorders of which liquid stools occurred most frequently.

CONCLUSIONS:

Four weeks of treatment with orlistat 120 mg tid with meals in addition to a hypocaloric diet did not change cholesterol saturation of bile or gallbladder motility compared with placebo and diet alone. Orlistat-treated subjects had unchanged bile acid composition whereas bile phospholipids, total bile acids, and the primary bile acid, cholate decreased in the placebo group. Orlistat and its primary metabolite M1 underwent biliary excretion. Four weeks of treatment with orlistat 120 mg tid was well tolerated in obese subjects.

Reviewer's Comments: Assay sufficiently cross validated for use in detecting orlistat and M1 in bile.

[redacted]

Appendix 1.5. Drug-Drug Interaction

Appendix 1.5.1. Antihypertensives (Pilot Studies)

Appendix 1.5.1.1. Influence Of Ro 18-0647 (THL) on Pharmacokinetics of Atenolol In Healthy Male Volunteers (P-7155)

VOLUME: 1.137

OBJECTIVES:
To investigate the influence of multiple dose treatment with THL (Ro 18-0647) 50 mg tid for 8 days on the absorption and disposition kinetics of atenolol in healthy male volunteers.

INVESTIGATOR/SITE:
[redacted]

FORMULATIONS:
Atenolol: (TENORMIN®) 100-mg tablet, batch no. 88 D 14
THL: hard gelatin capsule (Ro 18-0647/015, batch no. GMZ 657 D02) containing 50 mg THL

STUDY METHODS:
(a) Design: Open-label, sequential design with a single oral dose of 100 mg atenolol before (Day 1) and on the last day (Day 9) of multiple dose treatment with THL 50 mg tid for 8 days (Days 2 - 9).

(b) Demographics:

Gender (M/F)	Age (yr)	Weight (kg)	Origin
6/0	21-27	56-100	--

(c) Sampling times:
Days 1 and 9: plasma samples were collected at 0 h (predose); and 30, 60, 90, 120, 150 min, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 20, and 24 h postdose of atenolol.

ASSAY:
[redacted]

DATA ANALYSIS:
Paired t-test of atenolol pharmacokinetic parameters determined by model independent methods.

[redacted]
APPEARS THIS WAY ON ORIGINAL

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Clinical Pharmacology and Biopharmaceutics

Date: 06/26/97
From: Robert M. Shore, Pharm.D. /S/ 06/26/97
To: Maureen Hess
Re: Xenical® labeling

JUN 26 1997

Please note the following changes to the labeling:

(Page 2)
Pharmacokinetics:
DRAFT LABELING

(Page 10)
DRAFT LABELING

(Page 11)
DRAFT LABELING

cc: HFD-510(Colman, Hess, Hertig), HFD-870(Ahn, Shore, Fossler)

APPEARS THIS WAY ON ORIGINAL

HESS

MAR 21 1997

Clinical Pharmacology & Biopharmaceutics Review

NDA: 20-766	**SUBMISSION DATE:**	**November 26, 1996** **January 28, 29, 1997** **February 05, 10, 11, 1997** **March 05, 1997**
BRAND NAME:	**Xenical™**	
GENERIC NAME:	**Orlistat (Tetrahydrolipstatin [THL], Ro 18-0647) 120 mg oral capsules**	
REVIEWER:	**Robert M. Shore, Pharm.D.** **Michael J. Fossler, Pharm.D., Ph.D.**	
SPONSOR:	**Hoffman-La Roche, Inc.,** **Nutley, NJ**	
TYPE OF SUBMISSION:	**Original NDA (NME) Code: 1P**	

SYNOPSIS:

Hoffman-La Roche, Inc. has submitted NDA 20-766 for orlistat, a lipase inhibitor indicated for long-term weight control (weight loss, weight maintenance and prevention of weight regain) when used in conjunction with a mildly hypocaloric diet. The recommended dosage is one 120 mg immediate-release capsule orally three times daily with each meal (during or up to 1 hour after the meal). The 120 mg orlistat to-be-marketed formulation is identical to the clinical formulation used to conduct most Phase II and Phase III clinical studies except for the color of and imprint upon the capsule, the manufacturing equipment size, and manufacturing site. Bioequivalence (as pharmacological equivalence) of the final market formulation and the investigational formulations has been demonstrated. Systemic exposure to orlistat, at therapeutic doses, is minimal (<5% of an oral dose) due to limited absorption and / or first pass metabolism to inactive metabolites; plasma concentrations of orlistat were often below LOQ.

In vitro, orlistat is highly (>99%) bound to plasma proteins (mostly lipoproteins and albumin), with minimal partitioning into erythrocytes. Two major plasma metabolites of orlistat have been identified: M1 (4-member lactone ring hydrolyzed), and M3 (M1 with N-formyl leucine moiety cleaved). Both M1 and M3 have weak systemic lipase inhibitory activity (1000- and 2500-fold less than orlistat, respectively) and are considered inactive metabolites. Other metabolites (M7, M9, M13), including shortening of the $C_{11}H_{23}$ sidechain and conjugation with glucuronic acid, have been detected in urine and account for about 2% of an orally administered dose. All identified metabolites have a hydrolyzed β-lactone ring and, consequently, are devoid of relevant activity as lipase inhibitors. Approximately 97% of an orally administered ^{14}C-orlistat dose was excreted in feces, 83% as unchanged orlistat. Orlistat, M1, and M3 were also subject to biliary excretion; however, quantitative biliary excretion of the absorbed amount is unknown.

Drug-drug interaction studies were performed with atenolol, captopril, furosemide, nifedipine, digoxin, oral contraceptives, phenytoin, warfarin, ethanol, glyburide, pravastatin, vitamins, and vitamin analogues (e.g. β-carotene).

An Emax dose-response (daily dose-fecal fat excretion) relationship has been established.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation II (OCPB / DPE-II) has reviewed NDA 20-766 submitted November 26, 1996, January 29, February 05, 10, 11, 1997. The overall Human Pharmacokinetic Section is acceptable to OCPB / DPE-II. The recommended dissolution method is Apparatus II at [redacted] rpm using 900 ml of 3% SLS in 0.5% NaCl, pH = 6.0. The recomended specification is Q=[redacted] Please convey the recommendation, comments 1-3 (p.21) and labeling comments (p.21) to the sponsor as appropriate. Comment 1 will not preclude approval of this NDA in respect to efficacy and safety; it is recommended that the sponsor conduct the post-approval drug-drug interaction study.

TABLE OF CONTENTS

Section	Page
SYNOPSIS	1
RECOMMENDATION	2
BACKGROUND	2
PROTOCOL INDEX	3
DRUG FORMULATION	5
DISSOLUTION	5
ANALYTICAL METHODOLOGY	6
HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES	8
Bioavailability / Bioequivalence	8
Pharmacokinetics	9
Metabolism	12
Dose and Dosage Form Proportionality	13
Special Populations	14
Drug Interactions / Binding Studies	14
Pharmacokinetic / Pharmacodynamic Relationships	19
COMMENTS TO BE SENT TO THE SPONSOR	21
INTERNAL COMMENTS:	21
LABELING COMMENTS	21

Study Summaries (p.25-85)
Revised Labeling (p.86-104)

(Appendices and Attachments available from DPE-II upon request)

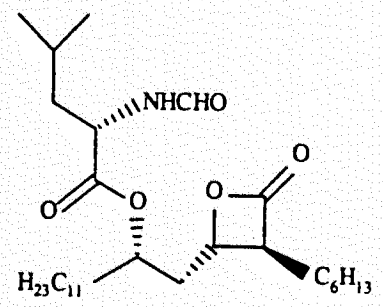
BACKGROUND:

Orlistat exerts its therapeutic activity in the lumen of the stomach and small intestine by forming a slowly reversible covalent bond with the active serine site on gastric and pancreatic lipases. Through this action, dietary fat in the form of triglycerides cannot be hydolyzed into absorbable free fatty acids and monoglycerides; these triglycerides, and sequestered cholesterol along with the triglycerides, pass through the intestines unabsorbed. This results in an overall decrease in absorbed calories.

Orlistat's empirical formula is $C_{29}H_{53}NO_5$, M.W. 495.75 (figure 1). It is poorly soluble in water at room temperature (< 1 mg/mL) and has a partition coefficient in octanol/buffer (pH 7.5) of log P = 4.40. Orlistat has no pKa value within the physiological pH range. Orlistat has 4 chiral centers and 2 polymorphic forms; the S,S,S,S stereoisomer with polymorphic form B is to be marketed.

In the phase II / III clinical trials where long-term safety, efficacy, and dose-effect relationship were studied, three dosage strengths (30, 60, and 120 mg) were studied. According to the sponsor, these trials indicated

that the dose of orlistat that produced clinical effect with the best overall safety profile was the 120 mg dose. Thus, for the market place, only the 120 mg strength will be available.



BEST POSSIBLE

Figure 1: Orlistat structure

There are 25 studies that have been identified as relevant to approval by the Office of Clinical Pharmacology and Biopharmaceutics, including: bioequivalence (1), plasma monitoring for orlistat and metabolites (6), mass balance (3), bile concentrations (1), and drug / vitamin interactions (14).

Orlistat is not currently commercially available in any part of the world.

PROTOCOL INDEX

Protocol Number (Study Report)	Title	Page
NP15400 (W145002)	Evaluation of the pharmacological equivalence of the orlistat (Xenical™ Ro 18–0647) formulation used in phase III studies with two final market formulations.	25
BM14150A (N138693)	The efficacy and tolerability of four doses of orlistat in the treatment of obesity after 24 weeks of treatment.	27
BM14119B (N138540)	The efficacy and tolerability of orlistat (120 mg tid) in the treatment of obesity after 52 weeks of therapy.	32
BM14119C (N138721)	The efficacy and tolerability of orlistat in the treatment of obesity after 104 weeks of therapy.	35
NM14161 (N138870)	The efficacy and tolerability of orlistat (60 mg and 120 mg tid) in the treatment of obesity after 104 weeks of therapy.	39
NM14336 (N138826)	A 57–week study of the effect of orlistat in the treatment of obese subjects with non–insulin dependent diabetes mellitus (NIDDM) maintained on oral hypoglycemic agents.	43
P-7166 (B116170)	Excretion balance and pharmacokinetic study with [redacted]C-labeled tetrahydrolipstatin [redacted] Ro 18-0647 / 004) after a single oral dose in healthy volunteers	48

NK14178A (N132323)	Pharmacokinetics of [redacted]C-labeled orlistat (Ro 18-0647) in healthy volunteers	49
NK14883B (N138422)	The metabolic profile of [redacted]C-labeled orlistat (Ro 18-0647) in obese volunteers	50
ND14278 (N138712)	Effect of multiple oral administration of Xenical™ (orlistat) on bile composition in obese subjects	50
P7155 (B116066)	Influence Of Ro 18-0647 [redacted] on pharmacokinetics of atenolol In healthy male volunteers	53
P7159 (B116072)	Influence of Ro 18-0647 [redacted] on pharmacokinetics of captopril in hospitalized healthy male volunteers	55
P7158 (B116067)	Influence Of Ro 18-0647 [redacted] on the pharmacokinetics of furosemide in healthy male volunteers	57
P7157 (B116064)	Influence of Ro 18-0647 [redacted] on the pharmacokinetics of nifedipine in hospitalized healthy male volunteers	59
NK14276A (N132254)	The effect of orlistat (Ro 18-0647) on the pharmacokinetics of digoxin in healthy volunteers	61
P5193 (B113407)	Interaction study with Ro 18-0647 and oral contraceptives	64
NK14574A (N138416)	The effect of Xenical™ (orlistat, Ro 18-0647) on the pharmacokinetics of phenytoin in healthy volunteers	66
NK14687B (N138392)	The effect of orlistat (Ro 18-0647) on the pharmacokinetics and pharmacodynamics of warfarin in healthy volunteers	68
BD14418 (N138588)	Interaction study with orlistat and ethanol	71
N3671B (N132009)	The effect of orlistat (Ro 18-0647) on the pharmacokinetics of glyburide in healthy volunteers	73
NK14856B (N138412)	The effect of Xenical™ (orlistat) on the pharmacokinetics of nifedipine extended release tablets (Procardia XL®) in healthy volunteers	75
BK14001A (B162079	Open, parallel group interaction study of Ro 18-0647 on the pharmacokinetics and pharmacodynamics of pravastatin in hospitalized healthy volunteers	77
NK14277A (N130970)	The effect of orlistat (Ro 18-0647) on the absorption of vitamins A and E in healthy volunteers	79
NK14179B (N132584)	The effect of orlistat (Ro 18-0647) on the absorption of β-carotene in healthy volunteers	81
BD14419 (W144991)	Effect of orlistat (Xenical™) or placebo treatment on pre- and post-heparin lipoprotein lipase (LPL) and hepatic lipase (HPL) activity following a fat-rich breakfast	83

DRUG FORMULATION:

[redacted]

Table 1. Xenical™ Formulation

Ingredient	Role	% [redacted]
Orlistat	[redacted]	
Microcrystalline Cellulose		
[redacted] Povidone		
Sodium Starch Glycolate		
Sodium Lauryl Sulfate		
[redacted]		
Talc		

[redacted]

DISSOLUTION:

[redacted]

[redacted]

ANALYTICAL METHODOLOGY:

[redacted]

APPEARS THIS WAY ON ORIGINAL

Table 2. LC/MS/MS for orlistat (Ro 18-0647) at [redacted]

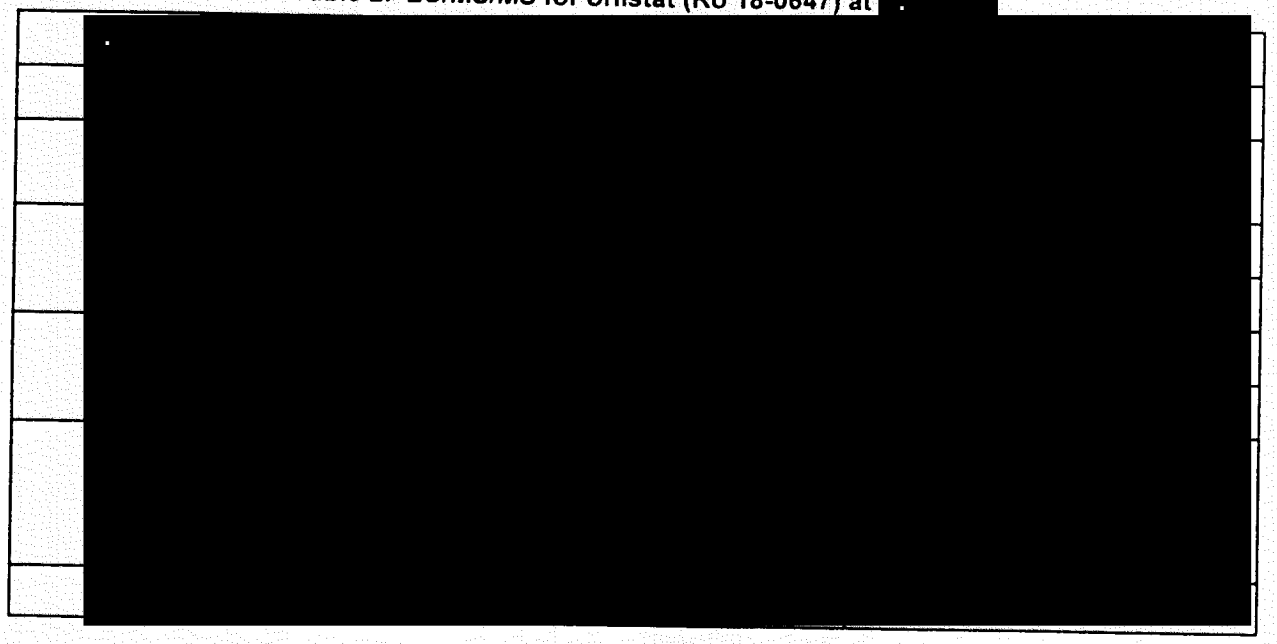
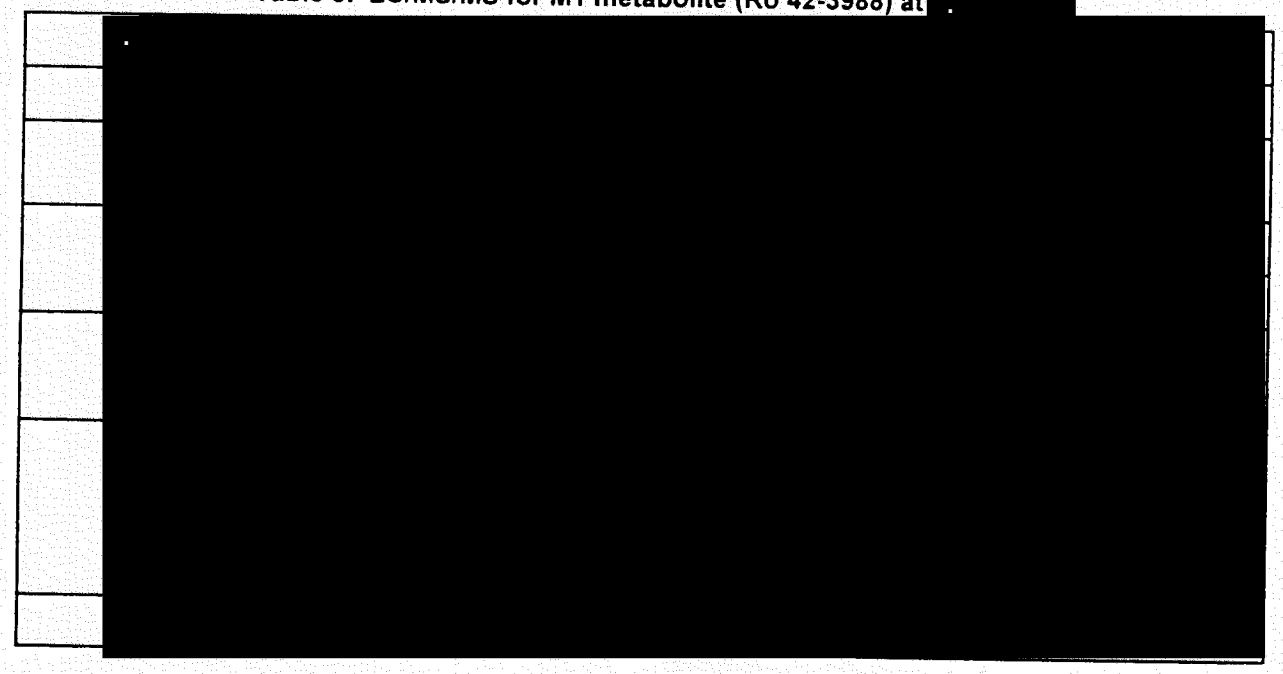
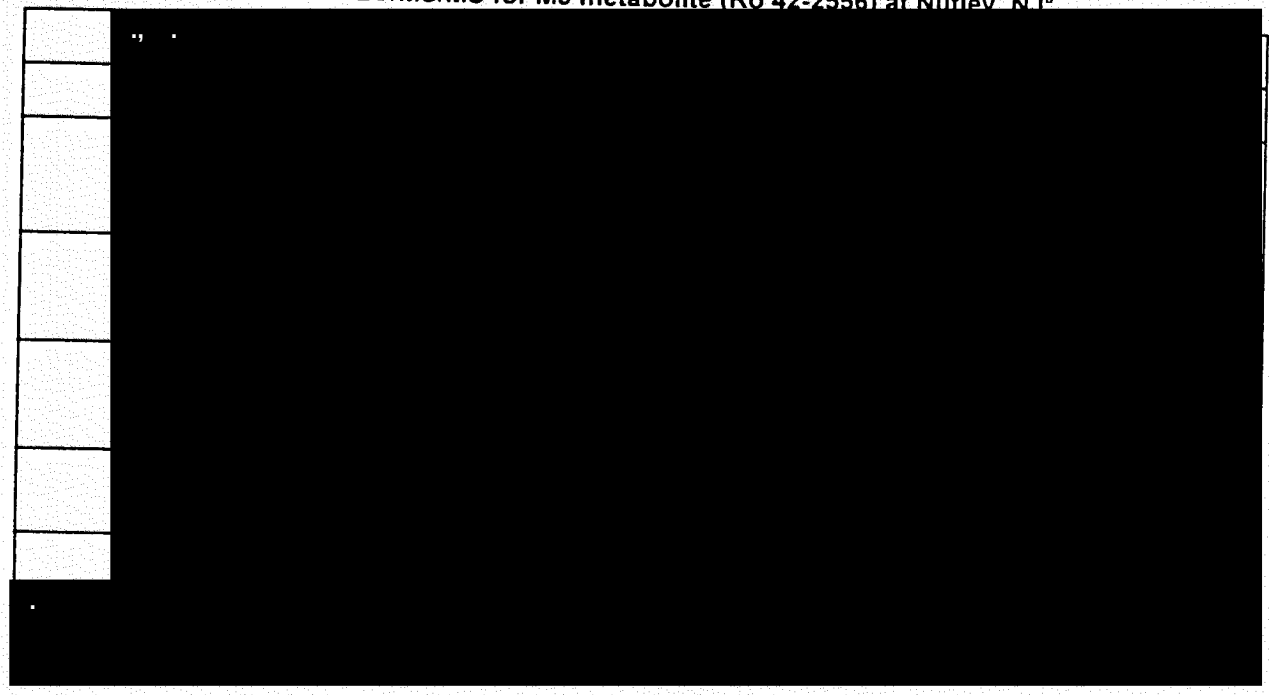


Table 3. LC/MS/MS for M1 metabolite (Ro 42-3988) at [redacted]



[redacted]

Table 4. LC/MS/MS for M3 metabolite (Ro 42-2556) at Nutley, N.J.[a]



HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:

I. Bioavailability / Bioequivalence

A. *Absolute Bioavailability*

As there is no acceptable IV formulation for use in humans, absolute bioavailability has not been determined.

There are several possible reasons for low plasma concentrations of orlistat, including: extensive first-pass metabolism and / or biliary excretion; low systemic absorption; large volume of distribution; and / or high systemic clearance. Animal studies using [redacted]C-labeled orlistat tend to indicate that orlistat does not undergo extensive tissue distribution and remains confined in the gastrointestinal tract. *In vitro* experiments are reported to have shown that orlistat has an IC50 of ~120 ng/mL for gastric and pancreatic lipases and ~300 ng/mL for plasma lipoprotein lipases; systemic orlistat exposure, at therapeutic doses, remains well below these concentrations.

B. *Bioequivalence*

Detectable plasma concentrations of orlistat, at therapeutic doses, are low and infrequent; as such, traditional pharmacokinetic data are not readily available. Therefore, fecal fat excretion had been proposed by the sponsor, and accepted by the agency (teleconference 12/11/95 with Drs. HY Ahn and ML Chen), as a pharmacodynamic endpoint for bioequivalence studies of the clinical and to-be-marketed formulations. An *in vivo* study (NP15400) was conducted to address whether the 120 mg formulations intended for either the European or U.S. markets were bioequivalent to that used in phase II / III trials. The primary parameter for the comparison of treatments was the change from baseline in mean 24 hour total fecal fat.

The least-squares means (LSMs) for the change from baseline in mean 24h fecal fat for groups A, B, and C