CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020766

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

20-766

Memorandum

ORIGINAL

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:	09-MAR-99
From:	Robert M. Shore, Pharm.D. /S/ 08-MAR-99
Through:	Hae-Young Ahn, Ph.D., Team Leader /S/ 3/9/99
To:	Maureen Hess,PM
Re:	NDA 20-766/N-000
	Xenical
	BL (labeling) submitted 21-JAN-99

Notes:

1. Referenced page numbers appear at the top right of the submission dated 21-JAN-99.

2. The sponsor's cover letter indicates that it is their understanding that the BL submission from 23-JUL-97 was not reviewed by the Agency. However, a review was done. Since that submission there have been no new submissions reviewed by the Office of Clinical Pharmacology and Biopharmaceutics. As such, the following comments are taken from the 23-JUL-97 review as well as the 03-JUN-97 BL review and the original NDA review.

3. Three new studies are included in this 21-JAN-99 submission. These drug-drug interaction studies (Xenical with simvastatin, atorvastatin and pravastatin[a repeat study]) have not been reviewed at this time and, thus, the results from these studies cannot be incorporated in the labeling.

SUBMISSION:

Four volumes have been submitted to the Office of Clinical Pharmacology and Biopharmaceutics. Volume 1 contains draft labeling and comments from the sponsor. Volumes 2 to 4 contain study reports from three drug-drug interaction studies (DDIS). None of these DDIS (Xenical with simvastatin, Xenical with atorvastatin, and Xenical with pravastatin) has been reviewed at this time. However, the pravastatin DDIS is the second such study; the original NDA contained a DDIS with pravastatin and the sponsor wishes to replace those data already sited in the labeling with this new data.

COMMENTS TO BE SENT TO THE SPONSOR:

Double underlined text is to be added; ~~strikeout text~~ is be removed; **bolded boxed text** is for explanation only and is not intended to be incorporated into labeling.

Vol. 1 / Page 2, Issue 2;

DRAFT LABELING

Rats received orlistat doses from 125 to 1000 mg/kg/day. The sponsor compared the average orlistat AUC0-24 at a dose of 150 mg/kg/day (230 ng•h/mL, n=3, CV%=N/A) to that from a 27.8 mg/kg IV dose (average AUC0-t of 36400 ng•h/mL, n=8, CV=24%). This low oral dose results in an average absolute bioavailability of intact orlistat of about 0.12%. When a 1000 mg/kg/day oral dose (average AUC0-24 of 7690 ng•h/mL, n=3, CV=N/A) is used, the average absolute bioavailability is about 0.59%

Dogs received orlistat doses of 100 and 1000 mg/kg/day. The sponsor compared the orlistat average AUC0-24 at a dose of 100 mg/kg/day (731 ng•h/mL, n=4, CV=82%) to that from a 5.1 mg/kg IV dose (average AUC0-t of 5570 ng•h/mL, n=3, CV=35%). This low oral dose results in an average absolute bioavailability of intact orlistat of about 0.7%. When the 1000 mg/kg/day oral dose (average AUC0-24 of 21100 ng•h/mL, n=4, CV=29%) is used, the average absolute bioavailability is about 1.9%.

Ref.: Vol. 20, p. 98-116 (Preclinical PK summary)
Vol. 77, p. 129, 130 (Dog oral data)
Vol. 107, p. 142, 143 (IV data)
Vol. 108, p. 45 (Rat oral data)

Vol. 1 / Page 2;

DRAFT LABELING

[redacted]

Since the three drug-drug interaction studies submitted in the 21-JAN-99 submission have not yet been reviewed, data from them cannot be incorporated into the labeling. The original pravastatin study data should be retained in the labeling.

Vol. 1 / Page 13, issue 20;

Agree with sponsor's re-location and wording for cyclosporin.

Vol. 1 / Page 14;

Drug Interactions:

Remove atorvastatin and simvastatin paragraphs (issue 22) because these studies have not yet been reviewed.
Cyclosporin (issue 20) is acceptable.

Vol. 1 / Page 15;

DRAFT LABELING

[redacted]

DRAFT LABELING

Although there was a drug-drug interaction study with Xenical and vitamin A submitted in the original NDA, the study was deemed unacceptable because the vitamin A dose given was not large enough to raise levels significantly above baseline.

Vol. 1 / Page 15, issue 24;

DRAFT LABELING

The new Xenical-pravastatin study has not been reviewed at this time. The original pravastatin study data should be retained in the labeling.

Vol. 1 / Page 28 (Patient package insert);

Can I take XENICAL while on other medications?

DRAFT LABELING

Although this statement may be true, there has been no analysis submitted of the clinical study data which examined the possibility of drug interactions. This statement may be taken to mean that there were no drug interactions in the clinical studies when Xenical was concomitantly administered with other drugs. Since this statement has no benefit in this labeling, and may lend a false sense of 'safety' to the patient when taking Xenical with other drugs, the Agency recommends removing this statement.

CC: NDA 20-766/N-000 (orig.,1 copy), HFD-510(Colman, [redacted]s, Hertig), HFD-340 (Vishwanathan), HFD-870(Fossler, Kavanagh, Ahn, ChenME), CDR (Barbara Murphy).

APPEARS THIS WAY ON ORIGINAL

+ LESS

JUL 31 1997

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA: 20-766	SUBMISSION DATE: 07/23/97
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:	BL; Labeling amendment

JUL 31 1997

*Note: referenced page numbers appear at the top of the submission dated 07/23/97.

Page 3;

DRAFT LABELING [redacted]

Rats received orlistat doses from 125 to 1000 mg/kg/day. The sponsor compared the average orlistat AUC0-24 at a dose of 150 mg/kg/day (230 ng•h/mL, n=3, CV%=N/A) to that from a 27.8 mg/kg IV dose (average AUC0-t of 36400 ng•h/mL, n=8, CV=24%). This low oral dose results in an average absolute bioavailability of intact orlistat of about 0.12%. When a 1000 mg/kg/day oral dose (average AUC0-24 of 7690 ng•h/mL, n=3, CV=N/A) is used, the average absolute bioavailability is about 0.59%

Dogs received orlistat doses of 100 and 1000 mg/kg/day. The sponsor compared the orlistat average AUC0-24 at a dose of 100 mg/kg/day (731 ng•h/mL, n=4, CV=82%) to that from a 5.1 mg/kg IV dose (average AUC0-t of 5570 ng•h/mL, n=3, CV=35%). This low oral dose results in an average absolute bioavailability of intact orlistat of about 0.7%. When the 1000 mg/kg/day oral dose (average AUC0-24 of 21100 ng•h/mL, n=4, CV=29%) is used, the average absolute bioavailability is about 1.9%.

Ref.: Vol. 20, p. 98-116 (Preclinical PK summary)
Vol. 77, p. 129, 130 (Dog oral data)
Vol. 107, p. 142, 143 (IV data)
Vol. 108, p. 45 (Rat oral data)

DRAFT LABELING [redacted]

All ^{14}C-orlistat studies reviewed utilized oral dosing.

Page 4;

DRAFT LABELING [redacted]

Page 24;

[redacted]

Page 26-27;

Any statement regarding steatorrhea and mineral balance.

As the mineral balance study has not been reviewed by The Office of Clinical Pharmacology and Biopharmaceutics, the Medical Division's decision will be final regarding this statement.

Robert M. Shore, Pharm.D.,
Michael J. Fossler, Pharm.D., Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

/S/ [redacted] 07/30/97

7/31/97

RD reviewed by Hae-Young Ahn, Ph.D., Team Leader 07/30/97

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ [redacted] 7/31/97

cc: NDA 20-766 (orig.,1 copy), HFD-510(Colman, Hess, Hertig, Haber), HFD-340 (Vishwanathan), HFD-870(Shore, Fossler, Ahn, M.Chen), CDR (Barbara Murphy).

/S/ [redacted]

[redacted]

HESS

JUL 25 1997

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA: 20-766	**SUBMISSION DATE:**	**06/03/97(BL)**
BRAND NAME:	**Xenical™**	
GENERIC NAME:	**Orlistat (Tetrahydrolipstatin [THL], Ro 18-0647) 120 mg oral capsules**	
REVIEWER:	**Robert M. Shore, Pharm.D.**	
SPONSOR:	**Hoffman-La Roche, Inc., Nutley, NJ**	
TYPE OF SUBMISSION:	**Labeling amendment**	

RECOMMENDATION:

Please forward the following labeling changes to the sponsor:

(Page 2)

DRAFT LABELING [redacted]

The animal data was reviewed by Pharm/Tox. OCPB and Pharm/Tox are of the opinion that the absolute bioavailability of orlistat is dependent on the specie of animal and dosage form used.

(Page 4)

DRAFT LABELING [redacted]

400 mg was not a 'cut-off' but rather an approximate dose at which the dose-response curve tended to plateau.

(Page 10)

DRAFT LABELING [redacted]

This provides a reason for the statement and may serve as a warning for other drugs which depend on fat for absorption.

(Page 11)

DRAFT LABELING [redacted]

DRAFT LABELING

This statement includes all available data.

/S/

Robert M. Shore, Pharm.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

07/25/97

/S/

FT initialed by Hae-Young Ahn, Ph.D., Team Leader 7/25/97

cc: NDA 20-766 (orig.,1 copy), HFD-510(Colman, Hess, Hertig, Haber), HFD-340 (Vishwanathan), HFD-870(Shore, Ahn, M.Chen), CDR (Barbara Murphy).

/S/

APPEARS THIS WAY ON ORIGINAL

Study Summaries

Revised Labeling

Appendix 1. INDIVIDUAL STUDY SUMMARY

Appendix 1.1.1. Synopsis of Research Report W–145002 (Protocol NP15400)

COMPANY: F. Hoffmann–La Roche Ltd. 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	Final Study Report – Protocol NP15400: Evaluation of the pharmacological equivalence of the orlistat (Xenical™ Ro 18–0647) formulation used in Phase III studies with two final market formulations. Research Report W–145002 / 18 October 1996.
INVESTIGATOR(S) / CENTER(S)	[redacted]
PUBLICATION	None
PERIOD OF TRIAL	28th July 1996 – 9th September CLINICAL PHASE I
OBJECTIVES	Primary: To compare the pharmacological activity (inhibition of fat absorption) of the 120 mg capsule formulation used in Phase III Clinical studies with the activities of two 120 mg capsule formulations intended for market use. Secondary: To monitor orlistat and its major metabolite plasma levels after administration of all formulations.
METHODOLOGY	Single centre, open–label, randomized, three–way crossover.

NUMBER OF SUBJECTS

Enrolled	No. eval. for			No. Prem. Disc. for		No. deaths
	PK	PD	Safety	AEs	Other reasons	
18	18	18	18	0	0	0

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Male and female obese volunteers.
TRIAL DRUG / STROKE (BATCH) NOs DOSE / ROUTE / REGIMEN / DURATION	During three 10–day periods between days 1 and 30: • 1 x 120 mg capsule orlistat, Ro 18–0647/J05 (F39), C186436 batch DB–26453–018B (US market formulation) • 1 x 120 mg capsule orlistat, Ro 18–0647/112, PT9268T05 (European market formulation) • 1 x 120 mg capsule orlistat, Ro 18–0647/090, PT2157T65 (Phase III formulation) 120 mg tid, PO, for 10 days
REFERENCE DRUG / STROKE (BATCH) NOs DOSE / ROUTE / REGIMEN / DURATION	None None
CRITERIA FOR EVALUATION EFFICACY: SAFETY: PHARMACOKINETICS: PHARMACODYNAMICS:	None. Adverse events, laboratory tests and vital signs. Plasma levels of orlistat and its primary metabolite. Change in 24–hour fecal fat excretion.

Appendix 1.1.1. (cont.) Synopsis of Research Report W–145002

(Protocol NP15400)

STATISTICAL METHODS — Analysis of variance, two one-sided

PROCEDURE:

This was a single-center, open label, randomized three-way crossover study in 18 obese subjects. During three 10 day periods (days 1-10, 11-20 and 21-30) the subjects received mid-meal 120 mg orlistat tid as A (120 mg US formulation), B (120 mg European formulation) and C (120 mg Phase III formulation) according to a randomized and balanced three-way crossover scheme. There was a 5 day run-in period before first administration of the drug, to accustom the subjects to a standardized diet with 2500 kcal/day containing 83 g (30%) of fat.

Feces were collected for determination of total fecal fat and blood samples were collected for determination of plasma orlistat and its major metabolite concentrations. Adverse events were recorded throughout the study.

PHARMACODYNAMIC RESULTS:

The least square mean for change from baseline in mean 24-hour fecal fat groups A, B and C were as follows: 25.38, 26.90 and 26.83, respectively. The ratio of the least square mean of treatments A/C and B/C were 0.95 and 1.00, respectively.

When the two market formulations were compared to the Phase III formulation using the confidence intervals for the ratio, both comparisons to the reference fell totally inside the range [0.80, 1.20]. It can therefore be concluded that the market formulations of orlistat were pharmacologically equivalent to the Phase III formulation.

PHARMACOKINETIC RESULTS:

There were no marked differences in the number of subjects with detectable plasma levels and in the orlistat plasma concentrations among the three treatment groups. The orlistat primary metabolite, M1, was measurable in all subjects with average values similar among the three formulations. Plasma levels of unchanged orlistat in the range of 0.21 to 3.33 ng/mL were detectable in 11 subjects in each group; means ±SD levels of its metabolite M1 (Ro 42-3998), for groups A, B and C were 45.46 ±21.57, 41.92 ± 19.39 and 40.08 ± 17.81 ng/mL respectively.

SAFETY RESULTS:

All the eighteen subjects reported at least one adverse event (AE) that was considered by the investigator to be remotely, possibly or probably related to the study medication and all were judged to be of mild or moderate intensity. Overall, a total of 100 AEs were reported; 34 during treatment A (in 14 subjects), 30 during treatment B (in 13 subjects) and 36 during treatment C (in 16 subjects). Over 50% of the adverse events related to the gastrointestinal tract (18, 14 and 18 AEs during treatments A, B and C, respectively) and were possibly or probably related to treatment. The most commonly reported adverse events were liquid stools (10 subjects), flatulence (9 subjects), abdominal pain (6 subjects) and nausea (5 subjects). Outside the gastrointestinal system, headache was the most frequent AE (9 subjects). None of the subjects withdrew from the study prior to completion and no treatment-related effects on laboratory parameters or vital signs were apparent.

CONCLUSIONS:

On the basis of the test parameters of fecal fat excretion, and on limited pharmacokinetics, the two formulations intended for market use were pharmacologically equivalent to the Phase III formulation. There were no differences in the safety profiles of the three formulations which were all shown to be well tolerated.

Reviewer's Comments: ANOVA was performed, accounting for the effects of sequences, subjects within sequences, time periods and treatments, and possible carryover effect from the preceding treatment. Treatments were compared pairwise using a 90% confidence interval for the ratio of treatment means. The reviewer repeated these comparisons using log-transformed ratios; similar results were found. Medi-Lab Fecal Fat assay information submitted: Conversion of all fecal fat (esterified, free, and salts) to free fatty acids, followed by quantitative titration with potassium hydroxide. Recovery >93%. Intra-day precision < 3%. Assay sufficiently validated. (RMS)

Appendix 1.2. Study Synopses of The Phase II/III Studies that Contain Pharmacokinetics

Appendix 1.2.1. Synopsis of Research Report N-138693 (Protocol BM14150A)

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	Final Study Report - Protocol BM14150A: The efficacy and tolerability of four doses of orlistat in the treatment of obesity after 24 weeks of treatment. Research Report N-138693 / July 9, 1996.
INVESTIGATOR(S) / CENTER(S)	[redacted]
INSTITUTION	
PUBLICATION	None
PERIOD OF TRIAL	February 16, 1994 - May 31, 1995 CLINICAL PHASE II
OBJECTIVES	- To determine the weight loss effect of 30 mg tid, 60 mg tid, 120 mg tid, and 240 mg tid of orlistat or placebo, in combination with a hypocaloric diet, administered for 24 weeks to obese patients. - To determine the tolerability of 30 mg tid, 60 mg tid, 120 mg tid, and 240 mg tid of orlistat administered for 24 weeks to obese patients.
STUDY DESIGN	Multicenter, double-blind, randomized, double dummy, placebo controlled, parallel design.

NUMBER OF SUBJECTS

	Randomized	Evaluated for Safety	Evaluated for Efficacy (ITT)	No. premature discont for AEs	other reasons	death
Placebo	125	124	123	3	24	0
30 mg tid	122	122	122	7	22	0
60 mg tid	124	123	123	6	23	0
120 mg tid	122	120	120	2	21	0
240 mg tid	120	117	117	3	17	0

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Obesity; including patients with a body mass index of 28 to 43 kg/m^2, men and nonpregnant females who are ≥18 years of age. Patients were excluded if they lost >4 kg in the 3 months prior to screen and if they had taken any drug which could influence body weight or plasma lipids during the 4 weeks prior to the placebo lead-in period.
TRIAL DRUG / STROKE (BATCH) NOs DOSE / ROUTE / REGIMEN / DURATION	30 mg orlistat capsules/ oral/ tid/ 24 weeks (Ro 18-0647/104)/Batch no. PT2182 T 01 60 mg orlistat capsules/ oral/ tid/ 24 weeks (Ro 18-0647/102)/Batch no. PT2159 T 17 120 mg orlistat capsules (2X for the 240 mg dose)/ oral/ tid/ 24 weeks (Ro 18-0647/090)/Batch nos. PT2157 T 51, PT2157 T 52, PT2157 T 53
REFERENCE DRUG / STROKE (BATCH) NOs DOSE / ROUTE / REGIMEN / DURATION	placebo (Ro 18-0647/103) to match the 30 mg and 60 mg capsules (Batch nos. PT2158 T 10, PT2158 T 11, PT2158 T 12) and placebo (Ro 18-0647/098) to match the 120 mg capsules (Batch no. PT2160 T 32) placebo/ oral/ tid/ 24 weeks
ANALYTICAL METHODS EFFICACY:	Changes in efficacy parameters from baseline (day 1) to Day 169 of the double-blind treatment period were used to measure efficacy and analysis of covariance and/or variance techniques were used for between treatment groups comparisons; pairwise comparisons were based on Holm's sequentially rejective Bonferroni test.
SAFETY:	Treatment groups were compared using descriptive statistics with respect to the following safety parameters: vital signs, laboratory tests, electrocardiograms and adverse experiences. Special analyses were carried out on plasma levels of vitamins A, D, E, β-carotene, prothrombin time and gallbladder ultrasound.

PROCEDURE:

Patients meeting the inclusion criteria entered a 4-week placebo lead-in period and were placed throughout the trial on a nutritionally balanced weight loss diet (600 kcal/day deficit). Following the 4-week placebo lead-in period, patients were randomized to receive either orlistat or placebo for 24 weeks. Treatment was administered as three capsules three times a day with meals. Throughout the study patients received dietary counseling and instructions on the use of diaries, and their compliance to diet was monitored. During placebo lead-in and first month of randomized treatment the patients visited the clinic every two weeks for assessment of tolerability, efficacy and dietary monitoring; from first month until the end of the trial the patient visited every month.

SUMMARY CONCLUSIONS

EFFICACY RESULTS:

Results for the primary efficacy parameter (body weight) are provided for the intent-to-treat (ITT) population in the table immediately below. Similar results were obtained for the ITT_{12wk}, Standard and Completers Populations. The 60 mg tid, 120 mg tid and 240 mg tid orlistat treatment groups had a statistically significant greater decrease in body weight than the placebo treatment group as measured by the least squares mean change in body weight from start of double-blind treatment to Week 24. Moreover, a greater proportion of orlistat-treated patients lost more than 10% of initial body weight than did placebo-treated patients.

Parameter	Placebo	30 mg tid	60 mg tid	120 mg tid	240 mg tid
	Change in Body Weight (ITT Population)				
Difference from placebo of least squares mean change in body weight from start of double-blind teatment	-	-0.95 (0.16)	-1.86 (0.002)	-2.55 (0.000)	-2.81 (0.000)
Mean % change (SD) from initial body weight at Week 24	-6.45 (5.84)	-8.49 (6.09)	-8.79 (5.99)	-9.76 (5.40)	-9.29 (5.82)
No. (%) patients losing >10% of initial body weight at Week 24	23 (18.7)	34 (27.9)	34 (27.6)	44 (36.7)	44 (37.6)

Results for the secondary lipid parameters are provided in the table immediately below. After 24 weeks of treatment, the least squares mean change in total cholesterol and LDL-cholesterol were statistically significantly lower ($p<0.05$) in each of the orlistat-treated groups compared with the placebo-treated group in the ITT Population. Although HDL-cholesterol levels increased in all treatment groups, the magnitude of the increase was significantly greater in the placebo group compared to each of the orlistat groups.

Parameter	Placebo	30 mg tid	60 mg tid	120 mg tid	240 mg tid
	Change in Serum Lipids (p-value; ITT Population)*				
total cholesterol (mmol/L)	---	-6.61 (0.000)	-7.16 (0.000)	-8.61 (0.000)	-10.11 (0.000)
LDL-cholesterol (mmol/L)	---	-6.08 (0.005)	-8.21 (0.000)	-11.02 (0.000)	-11.75 (0.000)
HDL-cholesterol (mmol/L)	---	-5.85 (0.007)	-7.03 (0.001)	-11.05 (0.000)	-10.36 (0.000)
triglycerides (mmol/L)	---	-1.40 (0.793)	-1.97 (0.714)	5.47 (0.307)	7.19 (0.183)
VLDL-cholesterol (mmol/L)	---	-0.06 (0.186)	-0.02 (0.739)	0.03 (0.532)	0.03 (0.595)
LDL/HDL ratio (mmol/L)	---	-0.06 (0.450)	-0.08 (0.274)	-0.03 (0.695)	-0.09 (0.228)

*Difference from placebo of least squares mean percent change in serum lipids from start of double-blind treatment to Week 24.

SAFETY RESULTS:

In general, adverse events were mild to moderate in intensity and the majority were judged by the investigator to be unrelated or remotely related to treatment. The percentage of patients with adverse events was dose-related: 79%, 83%, 84%, and 87% of patients in the 30 mg tid, 60 mg tid, 120 mg tid, and 240 mg tid dose groups, respectively. Sixty-nine percent of placebo-treated patients had adverse events. A greater proportion of orlistat-treated patients reported gastrointestinal (GI) adverse events (61% to 83% depending upon dose) than did placebo-treated patients (46%). The majority of these GI adverse events are potentially related to the pharmacologic effect of orlistat. These events include: fatty/oily stool, increased defecation, stools soft, flatulence, oily spotting, oily evacuation, fecal urgency, flatus with discharge and fecal incontinence. The majority of patients with these events reported one or two episodes. There were no deaths reported during the double-blind treatment period.

Serious adverse events were reported by two placebo-treated and 12 orlistat-treated patients during this 24 week study. The most common serious adverse event, abdominal pain, was reported in four orlistat-treated and none of the placebo-treated patients. All but one of these patients prematurely withdrew from study. The remaining serious adverse events were scattered among the various body systems and were not clustered in any particular treatment group.