

MEMORANDUM OF TELECON

DATE: April 15, 1997

APPLICATION NUMBER: NDA 20-766; Xenical

BETWEEN:

Name: Virginia Pate, Program Manager Drug Regulatory Affairs
Phone: (201) 562-3550
Representing: Hoffmann-La Roche

AND

Name: Maureen Hess
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Response to request for confirmation of waiver of Roche Basel Site Inspection

Informed Ms. Pate that an inspection of this site was not needed at this time because the firm meets criteria of the pre-approval inspection program. However, this does not mean that a waiver has been granted. At this time, an inspection assignment for this product has not been issued, but the process will be covered during the next inspection of the firm.

/s/

Maureen Hess, MPH, RD
Consumer Safety Officer

cc: Original NDA 20-766
HFD-510/Div. File
HFD-510/MHess/MHaber

APPEARS THIS WAY ON ORIGINAL

TELECON

NDA 20-766

Hoffmann-La Roche Inc.
Attention: Ms. Peggy Jack
340 Kingsland Street
Nutley, NJ 07110-1199

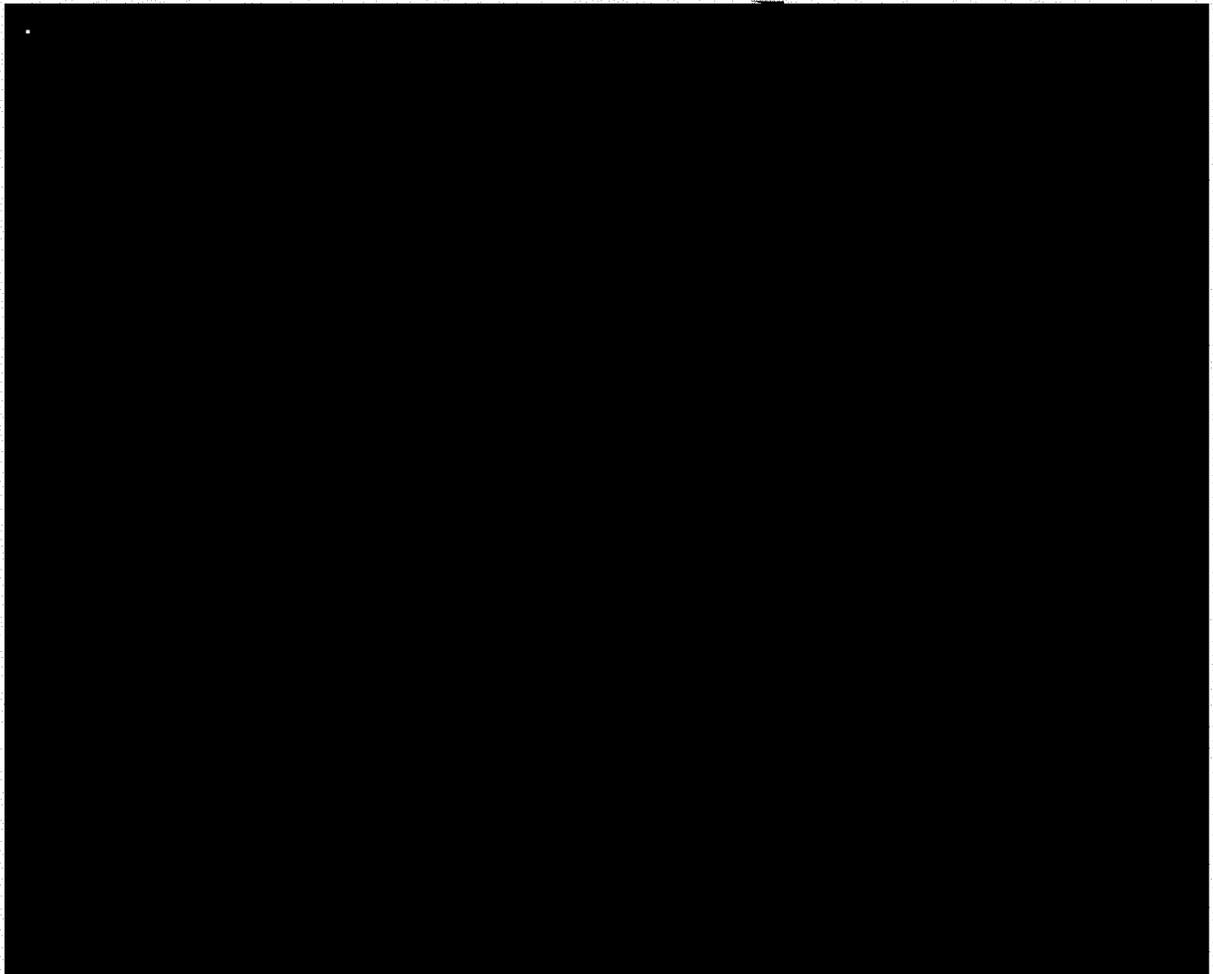
MAR 27 1997

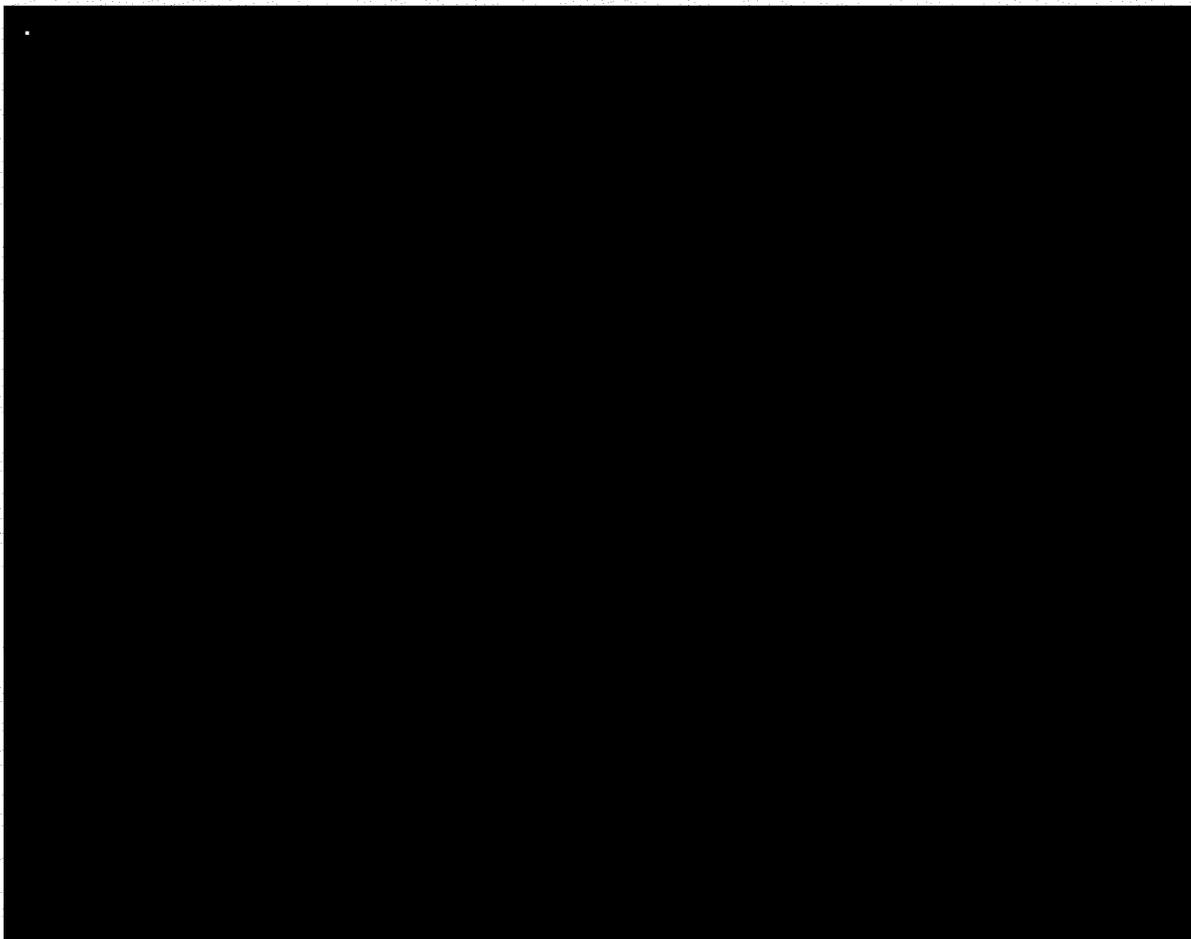
Dear Ms. Jack:

Please refer to your pending November 26, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xenical (orlistat) Capsules, 120 mg.

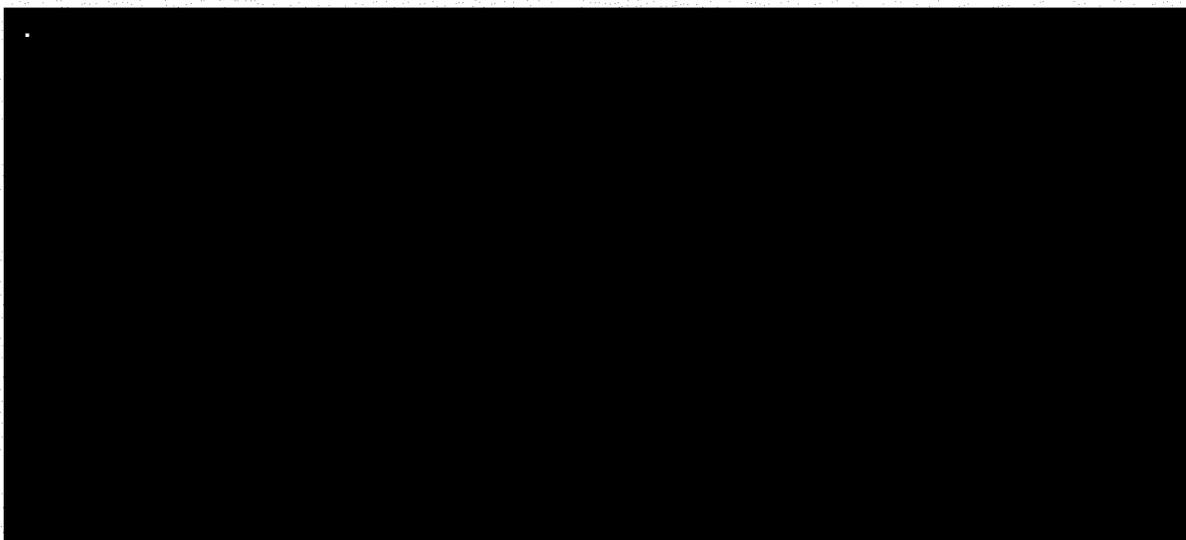
We have completed our review of the Chemistry and Biopharmaceutics sections of your submission and have the following comments and requests for information:

1. Regarding the Drug Substance:





2. Regarding the Drug Product:





3. Regarding Biopharmaceutics:

Although the warfarin-orlistat interaction study showed that orlistat had no effect on the pharmacokinetics of either stereoisomer of warfarin, the ratio of the K1 treatment means and 90% confidence interval (0.69 [0.39, 1.25]) suggest that there may be some adverse effect on K1 absorption. Based on the short duration of the study and the suggested effect on vitamin K absorption, an interaction with warfarin (based on affecting the absorption of vitamin K with a resulting increase in prothrombin time) cannot be ruled out. It is recommended that the labeling reflect this uncertainty (see Labeling Comments). In addition, we request a commitment to perform a post-approval study examining the effect of orlistat on plasma vitamin K and prothrombin time in patients on chronic warfarin therapy.

In addition, we have the following recommendations for changes to the label. We anticipate that more changes are forthcoming and request that you not submit a revised draft label at this time.

4. Labeling Comments:

- a. The dose of vitamin A used in Study N130970 was inadequate to raise retinol levels significantly above baseline, so no conclusions may be drawn from this study. In view of the ability of orlistat to decrease vitamin E and β -carotene absorption, it appears likely that it might also inhibit vitamin A absorption. It is recommended that the labeling reflect this conclusion (see Labeling Comments).
- b. As cyclosporin is dependent on dietary fat for adequate absorption, concomitant administration of orlistat and cyclosporin might be expected to decrease the absorption of cyclosporin, which could increase the risk of rejection in transplant patients. Although it is unclear whether orlistat would ever be prescribed in a transplant patient, the potential dire consequences of decreased cyclosporin levels suggests that orlistat be contraindicated in patients taking cyclosporin. This should be noted in the labeling.

CLINICAL PHARMACOLOGY

Pharmacokinetics:

Absorption: Systemic exposure to orlistat is [REDACTED] minimal. Following oral dosing with 360 mg ¹⁴C-orlistat, plasma radioactivity peaked at approximately 8 hours; plasma concentrations of intact orlistat were [REDACTED] near the limits of detection (<5 ng/mL). In therapeutic studies involving monitoring of plasma samples, [REDACTED]

., DRAFT LABELING

[REDACTED] detection of intact orlistat in plasma was sporadic and concentrations were [REDACTED] low (<10 ng/mL or 0.02 μM), without evidence of accumulation, and consistent with [REDACTED] minimal absorption.

Metabolism: Based on animal data, it is likely that the metabolism of orlistat occurs mainly within the gastrointestinal wall. Based on a ¹⁴C-orlistat mass balance study in obese patients, of the [REDACTED] fraction of the radio-labeled dose that was absorbed systemically, the presence of 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 systemic 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 2 to 4 hours after a dose, respectively), 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.

Drug-Drug Interactions: Orlistat had no effect on pharmacokinetics and/or pharmacodynamics of digoxin, phenytoin, warfarin, oral contraceptives, [REDACTED]

[REDACTED] Procardia XL, glyburide, [REDACTED] or alcohol. However, it enhanced the bioavailability and the lipid-lowering effect of pravastatin. Alcohol did not affect the pharmacodynamics of orlistat (see CLINICAL TRIALS and PRECAUTIONS).

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. E_{max} , the maximum attainable intensity of effect above baseline produced by XENICAL and presented as percentage of ingested fat excreted, was [REDACTED] 27% (95% CI: 21.5-32.8). ED_{50} , the XENICAL daily dose that produces 50% of the maximum effect, was [REDACTED] 98 (95% CI: 30.2-166.0) (mg/day). The dose-response curve demonstrated a steep portion for doses up to approximately 400 mg daily, followed by a plateau for higher doses. In doses above that recommended for therapy, the percentage increase in effect was minimal.

DRAFT LABELING
[REDACTED]

Drug Interactions: Alcohol: In a multiple-dose study in 30 normal weight subjects, coadministration of orlistat and 40 grams of alcohol (eg, approximately 3 glasses of wine) did not result in alteration of alcohol pharmacokinetics, orlistat pharmacodynamics (fecal fat excretion) and systemic exposure to orlistat.

Procardia XL: [REDACTED] In 17 normal weight subjects receiving XENICAL 120 mg tid for 6 days, XENICAL did not alter the bioavailability of Procardia XL [REDACTED].

DRAFT LABELING
[REDACTED]

Glyburide: In 12 normal weight subjects receiving XENICAL 80 mg tid for 4 1/3 days, XENICAL did not alter the pharmacokinetics or pharmacodynamics (blood-glucose-lowering) of glyburide. Weight loss induced by XENICAL is accompanied by improved metabolic control in diabetics, which might require a reduction in dose of oral hyperglycemic medication.

Pravastatin: In 24 normal weight, mildly hypocholesterolemic subjects receiving XENICAL 120 mg tid for 9 days, the effect of XENICAL was additive to the lipid-lowering effect of pravastatin. Modest increases (approximately 30%) in

pravastatin plasma concentrations were observed during coadministration with XENICAL.

DRAFT LABELING

Phenytoin: In 12 normal weight subjects receiving XENICAL 120 mg tid for 6 days, XENICAL did not alter the pharmacokinetics of [REDACTED] a single 300 mg dose of phenytoin.

Warfarin: In 12 normal weight subjects, administration of XENICAL (120 mg tid 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). **DRAFT LABELING**

[REDACTED] There is some indication that vitamin K absorption may be decreased with orlistat; patients on chronic stable doses of warfarin who are prescribed orlistat should be monitored closely for changes in coagulation parameters.

Digoxin: In 12 normal weight subjects receiving XENICAL 120 mg tid for 6 days, XENICAL did not alter the pharmacokinetics of a single dose of digoxin.

Oral Contraceptives **DRAFT LABELING**

DRAFT LABELING In 20 normal weight female subjects, the treatment of XENICAL 120 mg tid for 23 days resulted in no significant changes in the pharmacokinetics nor the ovulation-suppressing action of oral contraceptives.

Fat-soluble Vitamin Supplements and Analogues: A pharmacokinetic interaction study with β -carotene showed a 30% ~~one-third~~ reduction in β -carotene supplement absorption when concomitantly administered with XENICAL.

DRAFT LABELING XENICAL inhibited absorption of a vitamin E acetate supplement by approximately [REDACTED] 60%. **DRAFT LABELING**

The effect on vitamin A absorption is unknown; however, based on the above results XENICAL is likely to decrease its absorption as well.

As steatorrhea is known to increase the fecal loss of calcium, it appears likely that

orlistat will decrease the amount of calcium absorbed from the diet. The effect of orlistat on calcium supplementation (e.g., what percentage of the daily supplement dose is lost) is unknown.

During clinical studies based on the pharmacologic action of the drug there were decreases in levels of some fat soluble vitamins and analogues. The vast majority of patients in up to two full years of treatment had vitamin levels that stayed well within normal range, and there was no evidence of clinical sequelae.

DRAFT LABELING

Chemistry

- a. In the DESCRIPTION section, after the second sentence in the second paragraph which contains the empirical formula, please add the sentence, "It is a single diastereomeric molecule that contains four chiral centers, with a negative optical rotation in ethanol at 529nm."
- b. Draft carton labels must be submitted.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

APPEARS THIS WAY ON ORIGINAL

NDA 20-766
page 8

If you have any questions, please contact:

Maureen Hess, MPH, RD
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

 /SI

2/22/97

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

APPEARS THIS WAY ON ORIGINAL

Memorandum of Telecon

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

Date of Telecon: 03/10/97
From: Robert M. Shore
Re: Telecon about NDA 20-766 (Xenical®); request for information
Participants: Robert M. Shore (FDA)

Synopsis

I called Peggy Jack (201/235-4463). As she was not in, I left a voicemail requesting a reference for the claim in the proposed labeling (page 3) that the average plasma levels of M1 and M3 are 26 and 108 ng/mL, respectively.

cc: NDA 20-766 (orig., 1 copy), HFD-870 (Shore, Hess)

APPEARS THIS WAY ON ORIGINAL

Memorandum of Telecon

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

Date of Telecon: 02/27/97 [redacted]
From: Robert M. Shore
Re: Telecon about NDA 20-766 (Xenical®); request for information
Participants: Robert M. Shore (FDA); Peggy Jack (Hoffman-La Roche)

FEB 27 1997

Synopsis

I called Peggy Jack (201/235-4463) to clarify the site of manufacture of the final encapsulated product. Peggy explained:

1. The drug product, orlistat, was manufactured at [redacted] for the phase 1-3 clinical program, and will continue to be manufactured there for the to-be-marketed formulation.
2. For the clinical program, the Basle site also manufactured the final capsule, which were shipped to the US for use in the trials.
3. The to-be-marketed final capsule will be manufactured in Nutley, NJ, using the drug product from Basle.

cc: NDA 20-766 (orig., 1 copy), HFD-870(Shore, Hess)

APPEARS THIS WAY ON ORIGINAL

Memorandum of Telecon

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

Date of Telecon: 02/05/97
From: Robert M. Shore [redacted]
Re: Telecon about NDA 20-766 (Xenical[®]); request for information
Participants: Robert M. Shore (FDA); Peggy Jack (Hoffman-La Roche)

FEB - 5 1997

Synopsis

Peggy Jack called and I requested the following information:

1. Assay validation data (i.e. Was assay linear in the range studied? What was intra/inter-day variability? Was biological matrix of standards/QCs the same as sample matrix?) for two [redacted] studies, NK14178A and NK14883B. She stated that, from previous conversations with the agency, that it was the impression of the sponsor that this information was not required by the agency. I explained that assay validation, as far as I am concerned, is vital for any assay; She will make every effort to send this information ASAP.

cc: NDA 20-766 (orig.,1 copy), HFD-870(Shore)

APPEARS THIS WAY ON ORIGINAL

Memorandum of Telecon

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

Date of Telecon: 02/04/97 [redacted]
From: Robert M. Shore [redacted]
Re: Telecon about NDA 20-766 (Xenical®); request for information
Participants: Robert M. Shore (FDA); Peggy Jack (Hoffman-La Roche)

FEB - 4 1997

Synopsis

I called Peggy Jack (201/235-4463) and requested the following information:

1. Dissolution data: Vol 121 page 52(top) has some dissolution data, but I requested individual capsule dissolution data for 120 mg capsules,
2. Study report referenced in study NK14883B Volume 125 page 29(top), reference #4,
3. Volume 125 page 133 (top) - I requested more information on the [redacted] assay, as this is a very basic outline of the procedures,
4. The Medi-Lab fecal fat assay information that was submitted on January 29, 1997 included some QC data. However, there is no indication as to what the expected concentrations of these QCs were (e.g. only an observed mean and CV are reported). I requested further clarification on these QCs.

I mentioned that there may be more requests made, as this review has a very short time-frame for completion.

cc: NDA 20-766 (orig.,1 copy), HFD-870(Shore)

APPEARS THIS WAY ON ORIGINAL

Memorandum of Telecon

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

Date of Telecon: 01/29/97 [redacted]
From: Robert M. Shore [redacted]
Re: Telecon about Xenical® (NDA 20-766); request for information
Participants: Robert M. Shore (FDA); Tony Rhymer (Hoffman-La Roche)

JAN 29 1997

Synopsis

In response to a message left yesterday, Tony Rhymer of Hoffman-La Roche (201/235-2092) called. I requested the following information:

1. WordPerfect summary of Section 6, as discussed in the Pre-NDA meeting on Sept. 10, 1996. (According to a fax from the company, this has just been sent to the agency),
2. Study/report synopses from phase 2 and 3 studies, as requested in the Pre-NDA meeting,
3. Information on the fecal fat assay used in the pivotal bioequivalence studies, as discussed with Peggy Jack on January 06, 1997,
4. The Bioanalytical Report (BAR) No. B-556 from the Mass Balance study NK14178,
5. BAR for orlistat and the M1 metabolite from study NP14161 (Vol. 150),
6. Batch size for study NP15400 (Vol. 128, p.34) for batch C186436,
7. Information on the proposed dissolution spec. since Vol. 3, p.43-44 states Q= [redacted] while Vol. 121, p.132 states Q= [redacted]

I requested this information ASAP since this is a P drug and the Biopharm review must be done in less than a month. We agreed that the requested information would be sent "in pieces" - as available.

cc: NDA 20-766 (orig,1 copy), HFD-870(Shore)

APPEARS THIS WAY ON ORIGINAL

M. Hess

NDA 20-766

Hoffmann-LaRoche Inc.
Attention: Ms. Margaret J. Jack
Program Director
340 Kingsland Street
Nutley, NJ 07110

DEC 2 1996

Dear Ms. Jack:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

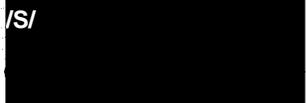
Name of Drug Product:	Xenical (orlistat) Capsules, 120 mg
Therapeutic Classification:	To be determined before the filing date
Date of Application:	November 26, 1996
Date of Receipt:	November 27, 1996
Our Reference Number:	NDA 20-766

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 26, 1997, in accordance with 21 CFR 314.101(a).

Should you have any questions concerning this NDA, please contact Maureen Hess, R.D., Consumer Safety Officer, at (301) 443-3490.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/s/ 

12-2-96

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Roche

Pharmaceuticals

April 5, 1999

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857-1706

Ladies and Gentlemen:

Re: **NDA 20-766 Xenical® (orlistat) Capsules, 120 mg**
Container Label and ADA Guidelines for OGTT Status

Reference is made to the teleconference today, April 5, 1999 regarding additional questions on the Oral Glucose Tolerance Testing in Obese Patients (OGTT) and the container label. The purpose of this submission is to respond to these additional questions.

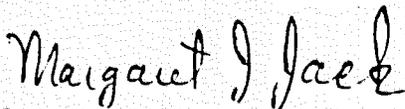
Regarding the OGTT in obese patients, the data included in the current Xenical labeling is based on the current ADA Guidelines which define normal, impaired and diabetic status using the two-hour datapoint.

Also included in this submission is the proposed container label for the bottles of Xenical capsules, bottle of 90 capsules with the following NDC number: NDC 0004-0256-52. This container label is in accordance with both the February 1998 and the July 1998 Guidance for Industry, "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997--Elimination of Certain Labeling Requirements." We note that the "Rx Only" is included on the container label; however, the July 1998 Guidance does not require this statement in the package insert labeling. This container label supercedes all versions of the Xenical container labeling previously submitted.

If you have any questions regarding the information included in the submission, please contact the undersigned at the numbers provided.

Sincerely,

HOFFMANN-LA ROCHE INC.



Margaret J. Jack
Program Director
Drug Regulatory Affairs
(973) 235-4463 (Telephone)
(973) 562-3554/3700 (Fax)

Attachments
HLR 1999-782
Desk Copy: Ms. Maureen Hess, CSO

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



Pharmaceuticals

April 1, 1999

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857-1706

Ladies and Gentlemen:

Re: NDA 20-766 Xenical® (orlistat) Capsules, 120 mg
Professional and Patient Labeling

Reference is made to the teleconference on March 22, 1999 and subsequent discussions on March 25, March 30 and April 1, 1999 regarding additional changes to the physician and patient labeling. This submission includes all the changes discussed as of April 1, 1999.

This submission includes both paper copies and disc with the professional package insert with all the requested revisions (accepted and annotated versions). This labeling supercedes all previous versions of the Xenical labeling and includes all corrections requested by the Review Division and Sponsor.

If you have any questions regarding the information included in the submission, please contact the undersigned at the numbers provided.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J. Jack

Margaret J. Jack
Program Director
Drug Regulatory Affairs
(973) 235-4463 (Telephone)
(973) 562-3554/3700 (Fax)

Attachments
HLR 1999-772
Desk Copy: Ms. Maureen Hess, CSO

March 30, 1999

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857-1706

Ladies and Gentlemen:

Re: **NDA 20-766 Xenical® (orlistat) Capsules, 120 mg**
Professional Labeling

Reference is made to the teleconference on March 22, 1999 during which the Agency and Sponsor reached agreement on the addition of Table 4 in the label which would include the weight loss and glycemic control data for the diabetes study (14336) and agreement on including the metabolic and cardiovascular risk factor data in text format in the label for the same study. On March 25 and March 30, 1999, the Agency provided additional comments on Table 4 which are included in this submission.

This submission includes both paper copies and disc with the professional package insert with all the requested revisions (accepted and annotated versions). This labeling supercedes all previous versions of the Xenical labeling and includes all corrections provided by the Review Division.

If you have any questions regarding the information included in the submission, please contact the undersigned at the numbers provided.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J. Jack

Margaret J. Jack
Program Director
Drug Regulatory Affairs
(973) 235-4463 (Telephone)
(973) 562-3554/3700 (Fax)

Attachments
HLR 1999-755
Desk Copy: Ms. Maureen Hess, CSO

March 26, 1999

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857-1706

Ladies and Gentlemen:

Re: NDA 20-766 Xenical® (orlistat) Capsules, 120 mg
Submission of Statistical Tables and Professional Labeling

Reference is made to the teleconference on March 22, 1999 during which the Agency and Sponsor reached agreement on the addition of Table 4 in the label which would include the weight loss and glycemic control data for the diabetes study (14336) and agreement on including the metabolic and cardiovascular risk factor data in text format in the label for the same study. On March 24, 1999 an initial draft of Table 4 and the above-mentioned text was faxed to FDA for review and comment and corrections to the Table 4 and text were provided to Roche on March 25, 1999. The Agency also requested that the printouts for the weight loss (intent-to-treat and completers) be provided in the future.

This submission includes both paper copies and disc with the professional package insert with all the requested revisions (accepted and annotated versions). This labeling supercedes all previous versions of the Xenical labeling. In addition, we are including Table 10 of the final study report for Protocol 14336 which includes the p-values for the difference in weight loss between Xenical and placebo from randomization for both the ITT and completers populations. The summary statistics tables (ITT and completers) for weight loss is also provided.

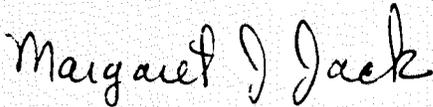
Please note the weight loss in the summary statistics tables is in kg, which were converted to lbs. for Table 4 of the PI by multiplying by the factor 2.2046. Because the summary statistics table provided for the completers population is from initial, the body weight from randomization is calculated using the difference between the values on day 1 and the end of 52 weeks of treatment and multiply by the 2.2046 factor.

Page 2
March 26, 1999

If you have any questions regarding the information included in the submission, please contact the undersigned at the numbers provided.

Sincerely,

HOFFMANN-LA ROCHE INC.



Margaret J. Jack
Program Director
Drug Regulatory Affairs

(973) 235-4463 (Telephone)
(973) 562-3554/3700 (Fax)

Attachments
HLR 1999-730

Desk Copy: Ms. Maureen Hess, CSO