NDA DRUG AMENDMENT ORIGINAL

B5

Roche Pharmaceuticals

A Member of the Roche Group

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

Direct Dial (201) 235-4463
Fax (201) 235-7771

/S/ [redacted]

January 28, 1997

CENTER FOR DRUG
REC'D
JAN 30 1997
HFD-510
EVALUATION AND RESEARCH

Dr. Kenneth Edmunds
Food and Drug Administration
Center for Drug Evaluation and Research, HFD-70
Room 8B45, Parklawn
5600 Fishers Lane
Rockville, MD 20857-1706

Dear Dr. Edmunds:

RE: NDA 20-766
XENICAL® (orlistat) Capsules, 120 mg
Delivery of CD-ROM Containing Requested SAS Datasets

The statistical reviewers for the above-mentioned application requested certain clinical data in electronic format, specifically on CD-ROM containing SAS datasets. The CD-ROM contains SAS v6.11 (for Windows NT/95) datasets, programs and reports. It has been scanned for and is free of known viruses.

The data and reports primarily correspond to the "Priority statistical analyses requested prior to NDA filing" as defined in a fax from the Division of Metabolic and Endocrine Drug Products dated January 9, 1997. Paper copies of the reports were submitted to the Agency on January 15, 1997.

Additional vitamin data not previously specified in the above-mentioned fax was requested by Dr. L. Pain (statistical reviewer) on behalf of the medical reviewer during a teleconference on January 23, 1997. This vitamin data is also included on the CD-ROM. To assist in understanding the vitamin data, programs and reports from the Xenical NDA Integrated Summary of Safety are also included.

The Word file **d:\thl\document\readme.doc** describes the directory structure used to store and link together data, programs and reports. The contents of the datasets are described in files to be found in subdirectories: of d:\thl\document as described in readme.doc .

Questions related to the datasets included on the CD-ROM should be addressed to:

Margaret J. Jack
Program Director
Drug Regulatory Affairs
☎: (201) 235-4463
Fax: (201) 235-7771

Dr. Jain Chung
Xenical Project Statistician
Department of Biometrics
☎: (201) 235-7241
Fax: (201) 562-3411

Should you have any questions regarding this submission, please feel free to contact the undersigned.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J. Jack

Margaret J. Jack
Program Director
Drug Regulatory Affairs

MMJ/LS:eh
HLR No. 1997-206
Desk Copies: Dr. Colman, Medical Review
Ms. Maureen Hess, CSO
Dr. L. Pain, Statistical Reviewer

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

DATE

CSO INITIALS

NDA ORIG AMENDMENT

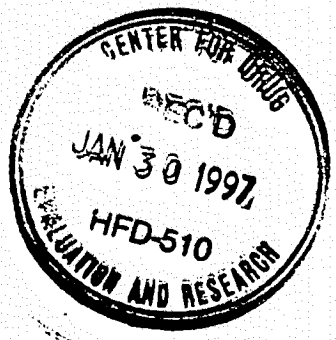
PS

Roche Pharmaceuticals
A Member of the Roche Group

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

Direct Dial (201) 235-4463
Fax (201) 235-7771

January 28, 1997



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
5800 Fishers Lane
Rockville, MD 20857-1706

Ladies and Gentlemen:

Re: NDA 20-766 Xenical®, 120 mg Capsules
Request for Statistical Portion of Animal Carcinogenicity
Data to be Provided in Electronic Format

Reference is made to the Agency's fax dated January 21, 1997 requesting the above-mentioned data to be provided in electronic format. The purpose of this submission is to provide the requested information.

The data from the 2-year oncogenicity studies conducted in mice and rats are provided on disk. Brief descriptions of the specific data formats for the oncogenicity studies in rats and mice are presented in Appendices A and B respectively. The data is provided on two disks, one disk containing the rat data and the other containing the data for the mouse study.

If there are any questions concerning this submission, please contact the undersigned at (201) 235-4463.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J. Jack

Margaret J. Jack
Program Director
Drug Regulatory Affairs

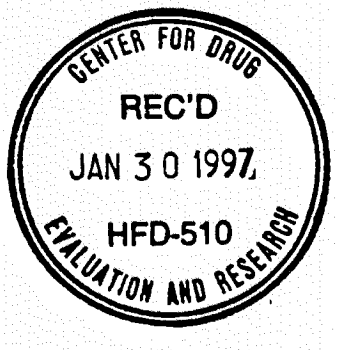
MMJ/LS:eh
HLR No. 1997-219

Roche Pharmaceuticals
A Member of the Roche Group

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

Direct Dial (201) 235-4463
Fax (201) 235-7771

January 28, 1997



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
5800 Fishers Lane
Rockville, MD 20857-1706

Ladies and Gentlemen:

Re: NDA 20-766 Xenical 120 mg Capsules
Additional Statistical Analyses Requested by the FDA
to be Submitted After the Filing of NDA 20-766

Reference is made to the January 7, 1997 teleconference between the sponsor and the Division to discuss the filability issues related to the above-mentioned NDA. Reference is also made to the fax dated January 9, 1997 from the Agency which included both specific analyses to be addressed by the sponsor before the filing of NDA 20-766 and included additional analyses and data which may be submitted after the filing of this NDA. The analyses needed prior to the filing of this NDA were provided in a submission dated January 15, 1997. The purpose of this submission is to provide this additional information and analyses not provided in the January 15 submission.

The additional statistical analyses requested by the statistician to be submitted after the filing of NDA 20-766 included:

1. Analyses of the four remaining Phase 3 studies

2. As an additional tool to investigate the effect of dropouts, please provide graphical displays for the various completer groups

The additional analyses requested by the medical reviewer to be submitted after the filing of NDA 20-766 included:

1. Statistical comparison of the following baseline (day 1) variables for each treatment group for the entire randomized population:

   - age
   - BMI
   - % female

- race
- systolic and diastolic BP
- lipid fractions
- fasting glucose and insulin
- fat soluble vitamins and beta carotene
- OGTT parameters
- % of patients with HTN and NIDDM (treated and non-treated)
- % of subjects receiving antihypertensive and lipid lowering medication
- average dose of oral hypoglycemic agent
- HbA1c

2. Statistical comparison of the following baseline (day 1) variables for each treatment group within the appropriate predefined risk-factor subgroup (i.e., HDL<0.905 mmol/L, SBP >140mmHg):

- fasting insulin
- LDL
- HDL
- triglycerides
- systolic BP
- diastolic BP
- waist circumference

The analyses requested in Number 1 (inquires from the statistical reviewer) for studies BM14149, BM14119B, NM14336 and NM14302 are provided in Appendices A, B, C and D respectively. Protocol BM14149 is a two-year study while the other three studies include one year of active treatment only.

Appendix A includes the summary statistics of treatment effects at weeks 24, 52, 80 and 104 for body weight (kg), % change in body weight and BMI for both the ITT and the ITT (observed) for Protocol BM14149. The supporting analysis of variance tables are also presented in Appendix A.

Appendices B, C and D include similar analyses at weeks 24 (week 28 for Protocol NM14302) and 52 for Protocols BM14119B, NM14336 and NM14302 as is presented in Appendix A for Protocol BM14149. It should be noted that Protocol NM14302 also includes the treatment effects for % regain of lost weight.

The graphical displays and supporting data requested in Number 2 are provided for the one-year and two-year data in Appendix E. In these graphs, the dotted line are the placebo groups and the solid lines represent the orlistat-treated groups.

Appendix E.1 includes the data for the intent-to-treat populations for patients who completed at weeks 12, 24, 36 and 52 for the 120 mg versus placebo and the 60 mg versus placebo treatment groups respectively, (--- placebo, — orlistat). The supporting tables for these graphs are presented in Appendix E.1.

Appendix E.2 contains the corresponding graphs and supporting data at weeks 60, 76, 92 and 104 for the intent-to-treat populations at the 120 and 60 mg doses respectively.

The additional analyses requested by the medical reviewer are presented in Appendices F through N respectively. Appendix F contains the statistical comparisons at baseline for the demographic data presented as follows:

Appendix F.1	-	Overall comparisons by individual studies, integrated summary of efficacy (ISE) year one and ISE two years; the year one data includes the 5 studies only and the two-year data includes the groups who received the same treatment for 2 full years.
Appendix F.2	-	120 mg versus placebo (ISE year one, ISE two years); the year one data includes the 5 studies only and the two-year data includes the groups who received the same treatment for 2 full years.
Appendix F.3	-	Non-US pooled (ISE year one, ISE two years) all doses; 120 mg vs placebo groups only, year one and two years
Appendix F.4	-	US pooled (ISE year one, ISE two years) all doses; 120 mg vs placebo groups only, year one and two years

Appendix G includes the statistical comparisons at baseline for secondary efficacy parameters presented in the following manner:

Appendix G.1	-	Systolic and diastolic blood pressures
Appendix G.2	-	Lipid fractions including total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides and LDL/HDL ratio
Appendix G.3	-	Fasting glucose and insulin
Appendix G.4	-	OGTT including glucose (AUC), insulin (AUC) and c-peptide (AUC)
Appendix G.5	-	Waist circumference

The statistical comparisons at baseline for vitamins A, D, E and beta carotene are presented in Appendix H respectively.

The statistical comparisons at baseline for % of patients with hypertension, NIDDM, % taking antihypertensive medications and % taking lipid-lowering medications are presented in Appendices I through L respectively. Additional comparisons for Protocol NM14336 including hemoglobin A1c and oral hypoglycemic agents are presented in Appendix M.

Appendix N includes the statistical comparisons at baseline for predetermined risk factor subgroups.

If there are any questions concerning this submission, please contact the undersigned at (201) 235-4463.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J Jack

Margaret J. Jack
Program Director
Drug Regulatory Affairs

MMJ/LS:eh
HLR No. 1997-207
Desk Copies: Ms. Maureen Hess, CSO (4)

2c ORIGINAL

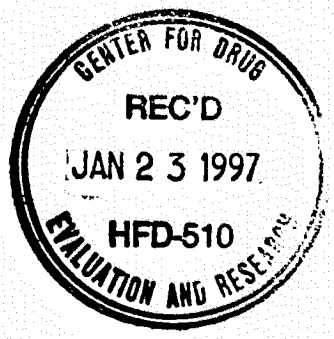
Roche Pharmaceuticals

A Member of the Roche Group

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

Direct Dial (201) 562-3550
Fax (201) 562-3700/3554

January 22, 1997



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, MD 29857-1706

Ladies and Gentlemen:

Re: NDA 20-766
XENICAL® (orlistat) Capsules
Response to FDA Telefax of January 9, 1997 (Chemistry)

Hoffmann-La Roche herewith is submitting a response to the inquiries concerning the Chemistry, Manufacturing, and Controls information for XENICAL® included in the above-mention NDA. These requests that were made during the January 7, 1997 teleconference with FDA, and outlined in page 2 of the January 9, 1997 telefax from Solomon Sobel, M.D., Director of the Division of Metabolism and Endocrine Drug Products. The telefax is included in Attachment I. The response to the telefax is as follows:

FDA Request:
Physical evidence should be provided to demonstrate that either the drug substance, Ro 18-0647, or key intermediate, Ro 19-3052, has the correct absolute configuration as described in the NDA submission.

[redacted]

FDA Request:
All facilities (including overseas) should be ready for inspection.

Roche Response:
All facilities mentioned in the NDA are actively involved in orlistat operations, and all will be ready for the pre-approval inspection by March 1, 1997.

The information contained in this correspondence is confidential and is not to be disclosed to any person outside the Food and Drug Administration without prior notification and written consent from Hoffmann-La Roche Inc.

Please feel free to contact the undersigned at (201) 562-3550 if you have any questions concerning this amendment.

Sincerely,

Hoffmann-La Roche Inc.
Virginia A. Pate
Virginia A. Pate
Program Manager
Drug Regulatory Affairs

VAP/LS:eh
Attachment
HLR No. 1997-134
Desk Copy: Ms. Maureen Hess, MPH, RD

Roche **Roche Pharmaceuticals**
A Member of the Roche Group

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

Direct Dial (201) 812-3719
Fax (201) 812-3700/3554

November 26, 1996

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, MD 20857-1706

Ladies and Gentlemen:

Re: NDA 20-766
XENICAL® (orlistat) capsules
Original New Drug Application

In accordance with 21CFR Part 314.50, Hoffmann-La Roche Inc. herewith is submitting an original New Drug Application (NDA 20-766) for XENICAL® (orlistat) 120 mg capsules, indicated for long-term weight control (weight loss, weight maintenance and prevention of weight regain) in conjunction with a mildly hypocaloric diet. The data included in this NDA demonstrates that XENICAL is effective for the long-term treatment of obese and overweight patients and for the improvement of risk factors associated with obesity. Orlistat has been the subject of IND [redacted] sponsored by Hoffmann-La Roche Inc., Nutley, NJ.

XENICAL is a potent, specific and long acting inhibitor of lipases. It exerts its therapeutic activity in the lumen of the stomach and small intestine by forming a covalent bond with the active serine site of gastric and pancreatic lipases. The inactivated enzymes are thus unavailable to hydrolyze dietary fat in the form of triglycerides into absorbable free fatty acids and monoglycerides. As undigested triglycerides are not absorbed, the resulting caloric deficit has a positive effect on weight control. Systemic absorption of the drug is therefore not needed for activity.

The information submitted in this NDA in support of the safety and efficacy of XENICAL has been derived from studies conducted under the above-mentioned IND and from non-US preclinical and non-IND clinical studies conducted under the auspices of F. Hoffmann-La Roche Ltd., Basel Switzerland.

The Phase 3 clinical program for XENICAL consisted of 7 multi-center, randomized, double blind, placebo-controlled trials of which four studies were 2 years of active treatment and three studies were 1 year of active treatment. One of the 1 year studies was conducted in obese patients with non-insulin dependent diabetes mellitus maintained on oral hypoglycemic agents and another

study was conducted in obese patients who lost 8% of their weight by diet alone in the 6 months prior to receiving 1 year of XENICAL therapy. The safety and efficacy data bases for the XENICAL Phase 3 clinical program are large consisting of over 2000 patients completing one year of XENICAL therapy and approximately 900 patients completing two years of XENICAL therapy. These seven studies are complete and all safety and efficacy analyses are included in this NDA.

The Phase 2 program consists of eleven double-blind, placebo controlled studies of which 7 studies were conducted in obese patients and four studies were conducted in mostly non-obese hypercholesterolemic patients. These studies were up to 6 months in duration. There were over 800 XENICAL treated patients in the Phase 2 program. All the data and analyses for these studies are included in this NDA.

The Phase 1 program consisted of 66 studies in which over 1,000 subjects received orlistat. These studies were up to 6 weeks in duration, and all these studies are included in the NDA.

The integrated safety summary includes all the safety data from the total clinical development program (Phase 1, 2 and 3) with the exception of one Phase 1 study which was completed after the integrated safety data base was closed. A complete study report for this study is in the NDA.

As per the sponsor's previous agreement with the Agency, Section 11 case report tabulations and summaries are not included in this submission due to the size of this section (approximately 1,300 volumes). These data can be retrieved on the CANDA for Phase 3 patients and the sponsor has agreed to provide any part of Section 11 on an as needed basis within 48 to 72 hours of the request.

The CANDA will be delivered to the Agency during the week of December 16, 1996 as per the sponsor's agreement with the medical reviewer, Dr. Eric Colman. The CANDA will include Phase 3 safety and efficacy data only, case report forms for death and dropouts due to adverse events for Phase 3, all clinical summaries, the final study reports for the seven Phase 3 studies and the proposed draft labeling for XENICAL.

As previously mentioned, all Phase 1, 2, and 3 clinical trials have been completed, and the data are in NDA 20-766. There is one ongoing Phase 3b trial being conducted in the UK with 50 hypercholesterolemic patients randomized to 120 mg t.i.d. XENICAL or placebo. The data from this trial are not available at this time.

As per the sponsor's previous agreement with the Agency, the 9-month data from a toxicology study conducted in rats maintained on a high fat/low calcium diet is not included in NDA 20-766. The data following the 3-month and 6-month interim sacrifices for this study are included in Section 5 and the 9 month data will be provided in the 4-month safety update.

A field copy containing a completed Form 3439, Section 3 (Application Summary) and Section 4 (chemistry, manufacturing and controls) of this NDA is being submitted simultaneously to the New Brunswick, NJ, District Office of the FDA. The undersigned hereby certifies that the copy submitted to the District Office is a true copy of that which is submitted to the Division of Metabolism and Endocrine Drug Products.

This submission consists of an archival copy (672 volumes) and required number of review copies. NDA 20-766 is organized as follows:

Section Number:	Volume No.
Section 1 - Index	**1**
Section 2 - Labeling	**2**
Section 3 - Application Summary	**3-4**
Section 4 - Chemistry, Manufacturing and Controls	**5-18**
Section 5 - Nonclinical Pharmacology and Toxicology	**19-120**
Section 6 - Human Pharmacokinetics and Bioavailability	**121-151**
Section 8/10 - Clinical and Statistical Data	**152-467**
Background and Overview Summary	152
Risk/Benefit Assessment	152
Drug Abuse and Overdose	152
Clinical Pharmacology Summary, Table of Studies, References	153
Phase II Controlled Trials - Obesity & Lipid Lowering Studies	236-277
Phase III Controlled Clinical Trials	278-452
Additional Efficacy and Safety Analyses of Phase III Data	453
Additional Safety Assessments by Consultants	454-456
Integrated Summary of Efficacy	457-460
Integrated Summary of Safety	461-463
Other references Cited in Section 8/10	464-465
Curriculum Vitae of Investigators	466-467
Section 11 Case Report Tabulations not provided	
Section 12 Case Report Forms, Deaths and Dropouts	**468-672**

Two desk copies of the Index (Section 1) for the entire NDA, labeling (Section 2) and the Application Summary (Section 3) are being provided directly to Ms. Maureen Hess, CSO in the Division of Metabolism and Endocrine Drug Products.

We understand that this New Drug Application and all information contained herein, unless otherwise made public by Hoffmann-La Roche Inc. is CONFIDENTIAL and will remain so subsequent to approval of the NDA for this drug. If for any reason Food and Drug Administration officials should at any time feel that disclosure of any of the materials contained in this NDA should be made public, Hoffmann-La Roche Inc. will be consulted first on the issue of disclosure.

As per Serial Submission No. 138 dated September 6, 1996 to IND 31,617, the sponsor is again requesting priority review of this NDA. The rational for priority review was provided in Serial Submission No. 138.

Please contact the undersigned at (201) 812-3719 by telephone or via fax at (201) 812 3700/3554 for any additional clinical or preclinical information concerning NDA 20-766 or IND [redacted] Any issues related to the chemistry, manufacturing, and controls of this compound may be addressed to Ms. Virginia A. Pate at (201) 812-3550.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J Jack

Ms. Margaret J. Jack
Program Director
Drug Regulatory Affairs

Attachments
MJJ:LS/jw
HLR No. 1996-2263
Desk Copies: Ms. Maureen Hess

about the possibility that the resubmission might not be filed. FDA replied that the fileability decision would be based on the amount of new information available, but that there is a high likelihood that the resubmission would be filed in this circumstance.

- HLR stated that it would like to have the breast cancer issue again discussed before an advisory committee, and questioned whether it would be feasible to consult with the oncology division and whether members of the oncology advisory committee might be involved in the discussion. FDA responded that it likely would agree to presenting this issue at another advisory committee meeting and that consultation with the oncology division seemed appropriate. Any advisory committee meeting held likely would include additional oncology experts, possibly some from the oncology advisory committee as well as non-advisory committee experts.

- HLR asked whether a resubmission would be reviewed within a 6-month time frame and FDA said it would.

- HLR stated that if another study is needed to clarify the breast cancer findings, a study is about to begin in Sweden. FDA will receive the protocol by 8/28, but, the investigators' meeting is scheduled for the weekend of 8/29 and HLR wants to proceed with the study. If FDA recommends substantial changes to the protocol, another study may be needed. In response to a question about the percentage of women receiving routine annual mammograms in the Swedish Health System, HLR said it would have to check on that. In response to a question whether the firm is committed to having screening mammograms for breast cancer done at baseline, HLR said yes, it is planning to do so at baseline with follow-up mammograms at two other times during the study. HLR plans to eliminate from the study those patients who have a diagnosis of breast cancer, but will leave in the study those who have a diagnosis of carcinoma in situ.

Decisions reached and action items:

- HLR will notify FDA by the end of the day regarding their intention of whether or not the new drug application for orlistat will be withdrawn. If a withdrawal decision is made, HLR will provide FDA with a copy of the press release for review regarding this action.

- HLR will provide FDA with the Swedish Study protocol for review.

Post-meeting action items:

- HLR withdrew the NDA for Xenical (orlistat) on August 27, 1997.

- Swedish study protocol provided for review; Division responded with written comments.

Signature, minutes preparer: /S/ [redacted]

Concurrence chair: /S/ [redacted] and /S/ [redacted]