Roche Pharmaceuticals
A Member of the Roche Group

Hoffmann-La Roche Inc.
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Direct Dial (201) 562-3550
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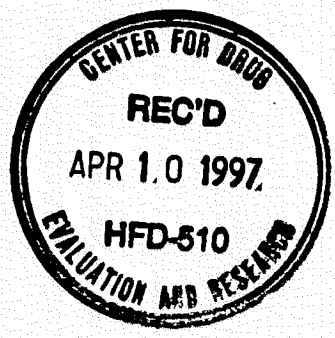
April 9, 1997

Ms. Maureen Hess, MPH, RD
Food and Drug Administration
Division of Metabolism and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857-1706



Dear Ms. Hess:

Re: NDA 20-766 Xenical®, 120 mg Capsules
Request for Confimation of Waiver of Roche Basel Site Inspection

Reference is made to Hoffmann-La Roche Inc.'s Original New Drug Application for Xenical (orlistat) Capsules, submitted on November 26, 1996. We were informed on April 7, 1997 by Dr. A. Kadar of the FDA International Office that an inspection of the Roche bulk manufacturing facility in Basel Switzerland will not be required for approval of the subject application. We hereby request confirmation of this decision from the Agency.

If there are any questions concerning this correspondence, please contact the undersigned at (201) 562-3550.

Sincerely,

HOFFMANN-LA ROCHE INC.

Virginia A. Pate

Virginia A. Pate
Program Manager
Drug Regulatory Affairs

VAP/LS:lh
HLR No. 1997-868

ORIGINAL

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Direct Dial (201) 235-4463
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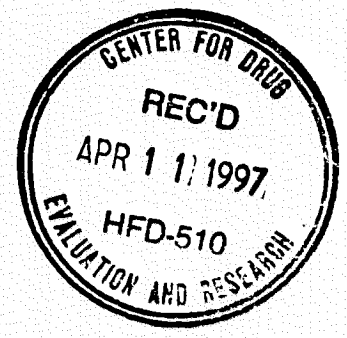
April 9, 1997



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, Maryland 20857-1706

Ladies and Gentlemen:

Re: NDA 20-766, XENICAL® (orlistat) Capsules
Four-Month Safety Update

We are herewith submitting the 4-month safety update for NDA 20-766 submitted November 27, 1996. The Phase 3 studies were completed, and the data for all patients was previously provided in NDA 20-766. Only errata identified in the database as of March 31, 1997 are provided in this safety update. The status of all ongoing clinical studies is also provided herein.

Reference is made to previous agreements with the Agency stating that the final study reports for the 9-month preclinical studies conducted in rats maintained on a high fat/low calcium diet to assess the effects of orlistat and diet on colonic mucosa in these animals were to be submitted in the 4-month safety update. The 6-month interim sacrifice data was included in Section 5 of the NDA. Final study reports for these studies are provided in volumes 2 through 5 of this submission.

This safety update for orlistat then specifically includes the following information:

1. Status of ongoing clinical trials, including the blinded data for the repeat mineral balance study, Protocol NP15491
2. Errata found in the Phase 3 clinical database
3. Final study reports for the above mentioned 9-month studies in rats
4. Revised Labeling

1. Status of Ongoing Clinical Studies

There are four ongoing clinical studies not reported in NDA 20-766. These include three Phase 1 studies of short duration, two of which were conducted in Europe and were not conducted under IND 31,617. The third Phase 1 study is Protocol NP15491 (repeat mineral balance study) for which the blinded mineral balance data is also provided. The clinical portion of these three Phase 1 clinical studies is complete and the analyses of the data is ongoing.

The fourth study is a Phase 3b study of one year duration being conducted in UK in obese hyperlipidemic patients, and patient enrollment is currently ongoing and expected to be completed by June of 1997. The clinical portion of this study is scheduled for completion in 1998.

Appendix 1. includes a more detailed description of these studies, their status and the blinded data for the mineral balance study. The unblinded data for this study is expected sometime in the latter part of April, 1997.

2. Errata Found in the Phase 3 Clinical Database

The Phase 3 clinical program was completed in March of 1996, and all patients who participated in the program were included in NDA 20-766 submitted November 1996. As of March 31, 1997 some errors have been identified in the clinical database which were not previously corrected in NDA 20-766. These errata are included in this 4-month safety update and include:

1. Marked Laboratory Abnormalities
2. Adverse Events
3. Serious Adverse Events
4. Reclassification of ECG Abnormalities
5. Adverse Events not included in the draft labeling presented in the NDA

Appendix 2. includes a detailed description of these errata.

3. 9-Month Rat Studies Addressing Effects of Orlistat and Diet Variables on Colonic Mucosa

Two 9-month studies in rats were conducted, one study with animals maintained on a high fat/low calcium diet (report number GCRN 139069) and the other study with animals maintained on a high fat/high calcium diet (report number GCRN 139068). A brief description of these studies in provided in Appendix 3 and the final study reports are in volumes 2 through 5.

4. Revised Labeling

The biopharmaceutic reviewers have requested that we not submit revised draft labeling until all the recommended labeling changes are provided (Agency fax dated 03/27/97), and since the safety data included in this report has minimal effect on the Xenical labeling, the sponsor will not be submitting revised draft labeling at this time. The sponsor is also currently revising the Xenical label to include vitamin supplementation and incorporating the suggested changes received to-date from the biopharmaceutic reviewers in the label and will submit these label revisions at the Agency's convenience.

If you have any questions concerning this submission, please contact the undersigned at (201) 235-4463 or via fax at (201) 235-7771.

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

MJJ/LS:rp
Attachments
HLR No. 1997-815

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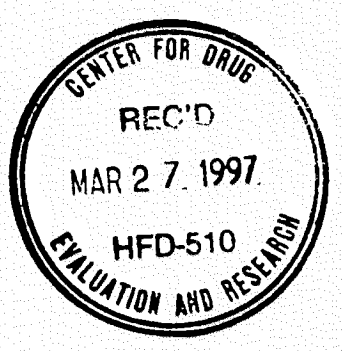
March 24, 1997

Dr. Eric Colman
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



Dear Dr. Colman:

Re: NDA 20-766 XENICAL® (orlistat) Capsules, 120 mg
Response to FDA's Request for Additional Analyses
1. Of Patients with DEXA Measurements and
2. Patients with Vitamin Supplementation

Reference is made to the requests for additional data and analyses of the patients with DEXA measurements conducted during the Phase 3 clinical program for orlistat at two study sites and for listings of how many patients required doubling of their vitamin supplementation during the first and second year of treatment and the statistical differences from placebo. The purpose of this submission is to provide some of the data requested for patients with DEXA measurements and to provide the information requested with respect to vitamin supplementation.

As previously mentioned, DEXA measurements were conducted at two study sites, one study site for Protocol BM14149 and one for Protocol BM14119C. DEXA measurements were conducted by Dr. L. Sjorstrom's study site in Sweden (BM14149) and by Dr. Anderson's study site in Denmark (BM14119C). We are herewith providing the data for Dr. Sjostrom's site including the following:

1. Demographics of the Study Site Population
2. Summary Tables of Weight Change
3. Summary Statistics of Vitamin D, A, E, Beta Carotene and Calcium
4. Estrogen Replacement Including:
    a. Female Patients Taking Estrogen at Baseline
    b. Female Patients Initiating Estrogen Therapy During the Study

These data are located in Appendix A of this submission. The data for Dr. Anderson's study site is currently being analyzed and will be provided in the very near future.

The vitamin supplementation data for patients requiring doubling of their supplementation is provided in Appendix B for the US studies only. This data is not available for the European studies.

If you have any questions concerning this submission, please contact the undersigned at (201) 235-4463 or via fax at (201) 235-7771.

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

MJJ/LS:lh
Attachments
HLR No. 1997-733

/S/

Roche Pharmaceuticals
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Direct Dial (201) 562-3550
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March 5, 1997

Dr. Michael Fossler
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

Re: NDA 20-766 Xenical®, 120 mg Capsules
Request for Additional Biopharmaceutical Information

ISI

Reference is made to your telephone call on February 18, 1987 requesting background information concerning the rationale for the use of [redacted]. The method was developed in Basel approximately eight years ago. The rationale for the choice of the dissolution medium is provided on the following page.

If there are any questions concerning this correspondence, please contact the undersigned at (201) 562-3550.

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Sincerely,

HOFFMANN-LA ROCHE INC.

Virginia A. Pate
Virginia A. Pate
Program Manager
Drug Regulatory Affairs

VAP/LS:lh
HLR No. 1997-552

ISI
19 Mar 97

Roche Pharmaceuticals
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340 Kingsland Street
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March 4, 1997

Dr. Lee Ping Pian
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

Dear Dr. Pian:

Re: NDA 20-766 XENICAL® (orlistat) Capsules, 120 mg
Information Requested by Statistical Reviewer
Lipid Data for Six Phase 3 Studies

As per your request, enclosed please find nine diskettes containing the lipid data sets for the following six Phase 3 studies: BM14119B, BM14119C, BM14149, NM14161, NM14185 and NM14336.

For each study there are two compressed SAS datasets, lipid.sd2 and lipid9.sd2, which are each located within a study-specific directory. Enclosed with this cover letter are explanations of the variables in the lipid and lipid9 datasets. The datasets are those from which the graphs and analyses of lipids were reported for each study.

The file compression was performed using PKZIP (Shareware version 2.50, Windows 32 bit). Included on a separate diskette are the necessary programs, virus scanned, to expand the files. Directions on how to install PKZIP are also provided.

If you have any questions concerning these data, please contact either Dr. Jain Chung at (201) 235-7241 or Dr. John Matheison at (201) 235-2332.

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

MJJ/LS
HLR No. 1997-542

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February 24, 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 20857-1706

Ladies and Gentlemen:

Re: NDA 20-766 XENICAL® (orlistat) Capsules, 120 mg
Response to FDA Request for Additional Subanalyses for
Weight Loss and Risk Factors Made February 21, 1997

Reference is made to your request for additional subanalyses for weight loss and risk factors made February 21, 1997. Specifically, additional analyses were requested for the three derived sub-populations of completers defined by the percentage of weight loss from baseline to the end of 1 year of treatment of 0 to <5%, 5 to <10% and >= 10%. The mean changes in risk factors (blood pressure, total cholesterol, LDL, HDL, triglycerides, fasting blood sugar and insulin) from baseline and initial value are presented for the placebo and orlistat 120 mg treatment groups for each of these three weight loss groups. The purpose of this submission is to provide these analyses as requested.

Appendix A

Appendix A is a summary table of patients with abnormal risk factors at baseline and the number (%) of those patients with normal values at the end of one year of treatment for the placebo and orlistat 120 mg treatment groups. These data clearly indicate that treatment with orlistat results in a greater percent of patients with normal risk factors at the end of one year treatment compared to placebo.

Appendix B

For the sub-population of patients with risk factors at baseline, the mean change from baseline for each risk factor for three weight loss subgroup (<5%, 5 to <10% and >= 10%) are presented in **Appendix B**. These baseline risk factors include:

LDL:	>= 3.362 mmol/L
HDL:	< 0.905 mmol/L
triglycerides:	>= 2.54 mmol/L
systolic bp:	>= 140 mm Hg
diastolic bp:	>= 90 mm Hg
insulin:	>= 90 pmol/L

Appendix C

The change from baseline for various risk factors for each of the three weight loss subgroups (<5%, 5 to <10% and >= 10%) are presented in **Appendix C** for the completers regardless of their risk factor status at baseline. Appendix C.1 is the hypothesis testing for the placebo vs the orlistat 120 mg groups for the various risk factors; Appendix C.2 are the supporting statistical tables and the summary statistics for all studies, the US population and the non-US population are presented in Appendices C.3, C.4 and C.5 respectively.

Appendix D

For the sub-population of patients with risk factors at initial value, the mean change from initial value for each risk factor for three weight loss subgroup (<5%, 5 to <10% and >= 10%) are presented in **Appendix D**. These risk factors include:

LDL:	>= 3.362 mmol/L
HDL:	< 0.905 mmol/L
triglycerides:	>= 2.54 mmol/L
systolic bp:	>= 140 mm Hg
diastolic bp:	>= 90 mm Hg
insulin:	>= 90 pmol/L

Appendix E

Appendix E includes the summary statistics for the change from the initial value for various risk factors for each of the three weight loss subgroups (<5%, 5 to <10% and >= 10%) for all studies (Appendix E.1), the US population (Appendix E.2) and the non-US population (Appendix E.3) respectively.

If you have any questions concerning this submission, please contact the undersigned at (201) 235-4463 or via fax at (201) 235-7771.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J Jack

Margaret J. Jack
Program Director
Drug Regulatory Affairs

MMJ/LS:rc
HLR No. 1997-470
Desk Copy: Dr. Eric Colman

Roche Pharmaceuticals
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Direct Dial
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February 11, 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 20857-1706

Ladies and Gentlemen:

Re: NDA 20-766 Xenical®, 120 Capsules
Request for References Cited in Study NP15138 in
Volume 215 pages 35 - 36 of NDA 20-766

As per your request, we are providing either copies of, or the location in NDA 20-766 for the nine references cited at the end of the above-mentioned study report. Two references were previously faxed to the Division on February 7, but copies of these two references are included in this submission with the copies of the other outstanding references.

If you have any question additional questions concerning this submission, please contact the undersigned at (201) 235-4463 or via fax at (201) 235-7771.

Sincerely,

HOFFMANN-LA ROCHE INC.

FOR Margaret J. Jack
Program Director
Drug Regulatory Affairs

MMJ/LS:eh
HLR No. 1997-352
Desk Copy: Ms. Maureen Hess, CSO

Roche Pharmaceuticals
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February 10, 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 20857-1706

Re: NDA 20-766 Xenical®, 120 mg Capsules
Request for additional Biopharmaceutical Information

Reference is made to your teleconference on January 31 with Dr. Anthony Rhymer requesting additional biopharmaceutical data to be provided. You requested the batch sizes and certificates of analysis for each lot (30 mg, 60 mg, and 120 mg capsules) used in the following trials: BM14149, BM14150A, BM14119B, BM14119C, NM14161, NM14185, NM14302, NM14336, BD14419, and ND14280. The certificates of analysis are attached. The batch sizes are noted on the certificates of analysis.

If there are any questions concerning this submission, please contact the undersigned at (201) 562-3550.

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Sincerely,

HOFFMANN-LA ROCHE INC.

Virginia A. Pate

Virginia A. Pate
Program Manager
Drug Regulatory Affairs

VAP/LS:eh
HLR No. 1997-334
Desk Copy: Dr. Robert Shore

Roche Pharmaceuticals
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February 10, 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 20857-1706

Ladies and Gentlemen:

Re: NDA 20-766 XENICAL®, 120 mg Capsules
Response to FDA Request for Information
Included in Fax dated January 29, 1997

Reference is made to the above-mentioned fax from the Agency requesting additional information on the Vitamins and Beta-Carotene, Study BM14119C, Study BM14149, and the Integrated Summaries of Efficacy and Safety to be provided for NDA 20-766. Reference is also made our submission dated February 5, 1997 which provided the responses to questions 1, 2, 3, 4, 5, 6, 7 and part of 13. Reference is also made to our fax dated February 7, 1997 which provided the answer to question 14 of the Agency's January 29, 1997 fax.

The purpose of this submission is to provide the answer to the remaining questions and to provide additional information for questions 5, 8, 11 and 13 included in the Agency's above mentioned fax.

As per the Agency's request, we are providing the information as it becomes available. For ease of review, we are providing a copy of the above-mentioned fax in which each question is enumerated and the corresponding responses are numbered accordingly. A copy of this fax with numbers assigned to each request for information is provided in Appendix A.

If additional information becomes available on any of theses questions, we will provide that information to the Agency in a timely manner.

[redacted]

If you have any questions concerning this submission, please contact the undersigned at (201) 235-4463 or via fax at (201) 235-7771.

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. 1997-340
Desk Copy: Dr. Eric Colman

NDA ORIG AMENDMENT 135 ORIGINAL

Roche Pharmaceuticals

A Member of the Roche Group

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Direct Dial (201) 235-4463
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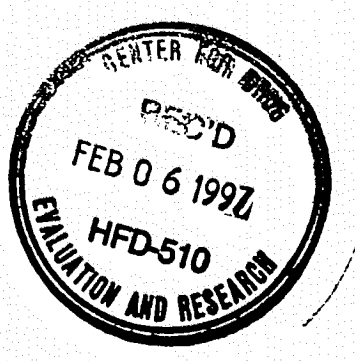
February 5, 1997



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 20857-1706

Ladies and Gentlemen:

Re: NDA 20-766 XENICAL®, 120 mg Capsules
Response to FDA Request for Information
Included in Fax dated January 29, 1997

Reference is made to the above-mentioned fax from the Agency requesting additional information on the Vitamins and Beta-Carotene, Study BM14119C, Study BM14149, and the Integrated Summaries of Efficacy and Safety to be provided for NDA 20-766.

As per the Agency's request, we are providing the information as it becomes available. For ease of review, we are providing a copy of the above-mentioned fax in which each question is enumerated and the corresponding responses are numbered accordingly. A copy of this fax with numbers assigned to each request for information is provided in Appendix A.

The additional responses will be provided in the near future when they become available.

If you have any questions concerning this submission, please contact the undersigned at (201) 235-4463 or via fax at (201) 235-7771.

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. 1997-308
Desk Copy: Dr. Eric Colman