HFD-104
VL-00

NDA 20-766

AUG 9 2000

Hoffmann-La Roche Inc.
Attention: Margaret J. Jack
Program Director
340 Kingsland St.
Nutley, NJ 07110-1199

Dear Ms. Jack:

Reference is made to your proposed Pediatric Study Request for Xenical (orlistat) Capsules submitted on March 17, 2000 to NDA 20-766.

We also acknowledge your amendment dated April 7, 2000.

To obtain needed pediatric information on orlistat, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

Study #1

Type of Study:

A double-blind, placebo-controlled, 54-week study (which includes a 2 week lead in period) of the efficacy and safety of orlistat in the weight management of obese pediatric patients.

Objectives:

To characterize the efficacy of orlistat as an adjunct to diet in the treatment of obesity in pediatric patients. To characterize the safety profile of orlistat in obese pediatric patients, including:

-Gastrointestinal tolerability
-Linear growth and Tanner pubertal stage assessment
-Bone mineral content and body composition measured by DEXA
-Fat-soluble vitamins, beta-carotene, PTH, and serum calcium levels
-Gall bladder and renal ultrasound

Indication to be studied:

Adolescent obesity

Study design:

A multicenter, randomized, double-blind, placebo-controlled, parallel study of obese adolescents. Approximately 450 pediatric patients should be randomized to receive either orlistat or placebo (2:1 randomization) as an adjunct to a hypocaloric diet, following a 2-week placebo lead-in period. All patients should receive nutritional and behavior modification counseling throughout the study. A multivitamin supplement should be prescribed for all patients.

Age group in which studies will be performed:

Ages 12 to 16 years.

Number of patients to be studied:

A total of approximately 450 patients should be enrolled into the study: approximately 300 to orlistat and approximately 150 to placebo. A reasonable distribution of patients in both treatment groups across the age range should be achieved. Each center should be expected to enroll approximately 15 patients.

Entry criteria:

Male and female patients who have a body mass index (BMI) at least two units greater than the U.S. weighted mean for the 95th percentile based on age and gender of any racial and ethnic groups will be eligible for study participation. Patients with mild chronic medical conditions such as hypertension, asthma, etc. who do not require treatment will be eligible for study participation. Exclusion criteria include:

-BMI > 44 kg/m^2 and/or body weight $\geq$ 130 kg
-body weight < 55 kg
-weight loss $\geq$ 3 kg within 3 months prior to screening

Clinical endpoints:

The primary endpoint should be change in BMI from baseline to Week 54 or study exit. Secondary endpoints should include change in body weight, linear growth, blood pressure, waist circumference, total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride levels, insulin and glucose levels at approximately 0 and 120 minutes after orally administered glucose stimulation.

Study evaluations:

Patients should have assessments of Tanner stage at baseline and at approximately Weeks 25 and 54 or study exit. Serum levels of sex-hormone-binding globulin, estradiol (females), and testosterone (males) should be measured at baseline and at approximately Weeks 25 and 54 or study exit. An electrocardiogram should be taken at baseline and at approximately Week 54 or

study exit. An assessment of changes in body composition should be obtained using DEXA at baseline and at approximately Week 54 or study exit.

Drug information:

- Dosage form: capsules
- Route of administration: oral
- Regimen: 120 mg or placebo three times per day with meals
- Formulation: same as marketed

Drug specific safety concerns:

The primary safety concerns are the effects of treatment with orlistat on serum levels of fat-soluble vitamins, linear growth, bone mineral content, and the risk for renal calculi and gallstones. Appropriate measures should be taken to monitor and assess these safety issues. An additional safety concern is the effect of orlistat on serum levels of various minerals. This will be addressed in a separate mineral balance study (see below).

Statistical information:

Assuming a 30% drop-out rate, 150 patients per group will provide 80% power at the two-sided 5% alpha level to detect a one BMI unit difference between treatment groups. The standard deviation of change from baseline BMI is estimated at 2.6. To provide additional safety information, approximately 300 patients should be randomized to the orlistat arm while approximately 150 patients should be randomized to the placebo arm.

All randomized patients who receive at least one dose of study medication and have a safety follow-up visit will be included in the safety analysis population. All randomized patients who receive at least one dose of study medication and have a follow-up visit for BMI will be included in the primary efficacy analysis.

Study #2

Type of study:

A 3 week study of the effect of orlistat on the balance of selected minerals in obese adolescents.

Objectives:

To assess the effect of orlistat (120 mg three times per day) on the balance of selected minerals in obese pediatric patients; to assess the effect of orlistat on plasma and urine electrolyte levels; and to evaluate the effect of orlistat on the extent of fat excretion.

Indication to be studied:

Not applicable.

Study design:

An in-patient, double-blind, placebo-controlled, randomized, parallel-group, 22-day study. All patients should receive a hypocaloric diet of about 1800 kcal, 30% of calories from fat, and maintain a constant daily mineral content.

Age group in which study will be performed:

Ages 12 to 16 years.

Number of patients to be studied:

A total of approximately 24 patients should be randomized in equal fashion to drug or placebo. A reasonable distribution of patients in both treatment groups across the age range should be achieved.

Entry criteria:

Healthy male and female patients with a BMI at or above the 85th percentile for age and gender with no major medical or psychiatric conditions.

Clinical endpoints:

Primarily, the balance of calcium, copper, iron, magnesium, phosphorus, and zinc. Also, serum and urine levels of sodium, potassium, and creatinine. Fecal fat content on approximately Days 15 and 21.

Study evaluations:

On approximately Days 10 to 22, all urinary and fecal output should be collected. Samples from approximately Days 15-22 should be stored for mineral analysis and fecal fat content determination as well as daily urinary creatinine and mineral output.

Drug information:

- **Dosage form**: capsules
- **Route of administration**: oral
- **Regimen**: 120 mg three times per day with meals
- **Formulation**: same as marketed

Drug specific safety concerns:

See *Study evaluations*.

Statistical information:

The pharmacodynamic parameters should be assessed for all patients who complete the study. Mineral balance data from approximately the last 7 days of treatment will be used for between-treatment comparisons. The 95% confidence interval will be used to estimate the difference between orlistat and placebo groups.

Labeling that may result from these studies:

Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of reports to be submitted: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.

Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before August 1, 2003. Please remember that pediatric exclusivity extends only existing patent protection or exclusivity that has not expired or been previously extended at the time you submit your reports of studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of

the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Maureen Hess, MPH, RD, Regulatory Health Project Manager, at (301) 827-6411.

Sincerely yours,

John K. Jenkins, MD
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Cc:
NDA 20-766
IND (b) (4)
HFD-510
/MHess/EColman/MHaber/DWu/DHertig/JElHage/HAhn/SMadani/LPian/TSahlroot
HFD-102/JJenkins/LRipper
HFD-600/Office of Generic Drugs
HFD-2/MLumpkin
HFD-104/Peds/DMurphy
HFD-104/Peds/TCrescenzi/VKao

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Initialed by:
LPian/6.5.00/TSahlroot/6.6.00/SMadani/5.23.00/HAhn/6.1.00/EColman/6.5.00/EGalliers/6.7.00/
LRipper/6.8.00 and 7.31.00/JJenkins/6.23.00 and 8.2.00
PDIT: 7.26.00 and 8.8.00
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PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)