DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-261
NDA 21-192

WRITTEN REQUEST

Novartis Pharmaceuticals Corporation
Attention: Adrian L. Birch
Executive Director, Drug Regulatory Affairs
59 Route 10
East Hanover, New Jersey 07936-1080

Dear Mr. Birch:

Reference is made to your Proposed Pediatric Study Request submitted on August 25, 2000, for Lescol XL (fluvastatin sodium) Tablets (NDA 21-192).

We acknowledge receipt of your submission dated March 16, 2001.

To obtain needed pediatric information on fluvastatin sodium, 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:

Type of study:

Study 1. An open-label trial in prepubertal boys with heterozygous familial hypercholesterolemia (heFH) that evaluates the effectiveness of fluvastatin sodium in reaching a defined LDL-C goal and evaluates its lipid-altering efficacy and overall safety at the maximum achieved dose for a minimum of approximately one-year duration.

Study 2. An open-label trial in children and adolescents (males and females) with heFH that evaluates the effect of fluvastatin sodium on reaching a defined LDL-C goal and evaluates the efficacy and safety at the maximum achieved dose with an average exposure at that dose of approximately 18-months duration.

Indication to be studied (objective/rationale):

To characterize the safety and to assess the effect of fluvastatin sodium on plasma lipids in children and adolescents with heFH.

Age groups in which studies will be performed:

Study 1. Male patients ages 9 through 12 years, inclusive.

Study 2. Female and male patients ages 10 through 16 years, inclusive.

Number of patients to be studied:

Study 1. Approximately 30 male patients treated with fluvastatin sodium must complete the study.

Study 2. Approximately 50 patients treated with fluvastatin sodium must complete the study. Enrollment should be targeted at treating more female patients than male patients in this study.

Entry criteria:

Study 1. Prepubertal males ≥ 9 years and ≤ 12 years of age with heFH defined as:

- primary hypercholesterolemia with LDL-C above the 90th percentile for age AND
- a parent with primary hypercholesterolemia and either a family history of premature ischemic heart disease or tendon xanthomas

Study 2. Males and females ≥ 10 years and ≤ 16 years of age with heFH defined as:

- LDL-C levels ≥ 190 mg/dL (4.9 mmol/L) OR
- LDL-C levels ≥ 160 mg/dL (4.1 mmol/L) and one or more risk factors for coronary heart disease OR
- LDL-C ≥ 160 mg/dL (4.1 mmol/L) and a proven LDL-receptor defect

Exclusion Criteria:

- Males with a testicular volume <3 cc after age 12.
- Pre-menarchal females. Post-menarchal females must have had at least three regular menstrual cycles.

Study endpoints and timing of assessments, including primary efficacy endpoints:

Primary efficacy variable: Percent change from baseline in LDL-C and proportion of patients achieving an LDL-C goal of ≤ 130 mg/dL. Valid efficacy assessments of LDL-C and other plasma lipids include values obtained at baseline and after at least 6 weeks of treatment. Secondary endpoints include other plasma lipids (total cholesterol, HDL-C, triglycerides) clinical and laboratory safety outcomes including serum transaminase and creatine kinase levels and adverse events to be assessed periodically on treatment, and developmental outcomes (height and Tanner stage) to be assessed at baseline and at end of treatment and/or at follow-up.

Drug information:

- ***Dosage forms:*** capsules and tablets
- ***Route of administration:*** oral
- ***Regimen:*** 20, 40, and 80 mg
- ***Formulation:*** same as marketed

***Drug specific safety concerns*:**

Studies 1 and 2.
Effects on liver and muscle as monitored by serum transaminase and creatine kinase levels. Effects on growth and sexual maturation as assessed by stadiometry and Tanner staging.

Study 1. Effects on growth and sexual maturation as assessed by bone age assessment, testicular size, and Tanner staging. Effects on endocrine function as assessed by measurement of testosterone, LH, FSH, DHEAS, TSH, and IGF-1.

Study 2. Effects on growth and sexual maturation as assessed by linear growth and Tanner staging. Effects on endocrine function as assessed by menstrual cycle monitoring, estradiol, LH, and FSH. In addition, pregnancy testing will be performed at baseline and at specified intervals during the treatment period in all female patients.

Statistical information, including:

Descriptive statistics will be reported for the primary efficacy variable and percentage of patients reaching LDL-C goal.

Descriptive statistics will be reported for the secondary efficacy variables.

***Labeling that may result from the 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 or analyses not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation, and with accompanying computer-based clinical and safety data listings. To satisfy the requirements for exclusivity, submit the safety and efficacy results of Study 1 and Study 2.

***Timeframe for submitting reports of the studies**:*

Reports of the above studies must be submitted to the Agency on or before December 2, 2005. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Please submit protocols for the above study 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, contact William C. Koch, R.Ph., Regulatory Project Manager, at (301) 827-6412.

Sincerely,

{See appended electronic signature page}

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Jenkins
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