DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

NDA 21-366

AstraZeneca Pharmaceuticals LP
Attention: Mark S. Eliason, MSc
Director, Regulatory Affairs
1800 Concord Pike
P. O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Eliason:

Reference is made to your November 17, 2005, Proposed Pediatric Study Request submitted to IND 56,385 for Crestor (rosuvastatin calcium) Tablets.

To obtain needed pediatric information on rosuvastatin calcium, 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 study:

- ***Type of study*:** The study should be designed as a randomized, double-blind, placebo-controlled, parallel group, 12-week study in adolescents with heterozygous familial hypercholesterolemia, who have failed dietary intervention. Patients should be randomized to one of four treatment arms; placebo, rosuvastatin 5 mg, 10 mg or 20 mg. At the end of the 12-week double-blind treatment period, all placebo patients remaining on study should be switched to 5 mg of rosuvastatin and titrated to an LDL-C goal of <110mg/dL over a 40-week open-label extension. Patients on rosuvastatin 10 or 20 mg who reach an LDL-C goal of < 110 mg/dl at the end of the 12-week double-blind treatment period should be switched to rosuvastatin 5 mg and titrated to maintain an LDL-C < 110 mg/dl. Patients originally randomized to rosuvastatin 5 mg or 10 mg who have not reached the LDL-C goal at the end of the double-blind treatment period should enter the open-label extension on their assigned treatment and then be titrated during this 40-week period to achieve an LDL-C < 110 mg/dl. Patients originally randomized to rosuvastatin 20 mg who have not reached the LDL-C goal at the end of the double-blind treatment period should remain on this dose throughout the 40-week open-label extension.
- ***Indication to be studied (i.e., objective of each study):*** Adjunct to diet to reduce Total-C, LDL-C and ApoB levels in adolescent boys and girls, who are at least one year post-menarche, 10-17 years of age with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy LDL-C ≥ 190 mg/dL or ≥ 160 mg/dL and there is a positive family history of premature cardiovascular disease (CVD) or two or more of the following CVD risk factors (cigarette smoking, elevated BP, HDL-C < 35 mg/dL, severe obesity, diabetes mellitus, or physical inactivity).
- ***Age group in which study will be performed*:** Children and adolescents ≥ 10 years and ≤ 17 years of age, Tanner stage II and above. Girls are to be at least one year post-menarche. Boys with testicular volume < 3cc after age 12 should be excluded for delayed puberty. Boys and girls with

height < 3rd percentile for age and sex or height-weight ratio > 97th percentile for age and sex should also be excluded. There must be a reasonable distribution of patients between the two genders and across the specified age range in both treatment groups. However, due to the exclusion criteria, it is recognized that it may not be possible to enroll a significant number of girls at the lower end of the age range.

- ***Study endpoints***

Primary Endpoint: Percent change in LDL-C from baseline to week 12 or the end of the double-blind portion of the study.

Secondary Endpoints:

1. Percent change in LDL-C from baseline to week 6.
2. Percent change in Total-C, HDL-C, non HDL-C, triglycerides, and ApoB from baseline to week 6, and week 12 or the end of the double-blind portion of the study.
3. Percent of patients who reach LDL-C goal (<110mg/dL) at week 52 or the end of the study with any dose (5-20 mg/day) of rosuvastatin.
4. Clinical and laboratory safety outcomes (including urinary protein/creatinine ratio, blood pressure), adverse events, and developmental outcomes (including linear growth [cm and Standard Deviation Score] and Tanner stage measured at baseline and end-of-study).

- ***Drug information***
  - ***Dosage form:*** Tablets
  - ***Route of administration:*** Oral
  - ***Regimen:*** 5 to 20 mg once daily
  - Use an age-appropriate formulation in the study(ies) described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.

    Development of a commercially-marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

    If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening

agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- ***Drug specific safety concerns*:**
  - Effects on proteinuria, as assessed by urinary protein/creatinine ratio from three consecutive first morning voids, should be assessed at baseline, at 12 weeks and 52 weeks or the end of study.
  - Effects on liver, muscle, and kidney as monitored by blood chemistries (including serum transaminases, creatinine kinase, and serum creatinine). Measurements should be made at randomization, week 2, week 6 and approximately every 6 weeks thereafter until the end of the study.
  - Effects on growth and sexual maturation as assessed by stadiometry (cm and SDS) and Tanner staging at baseline and at 52 wks or the end of study participation.

  A contingency plan must be included in the protocol describing how patients who have increases above the normal range in urine protein/creatinine ratios, creatine kinase, serum creatinine or blood pressure will be monitored. An external consultant should be included as part of the study protocol as an independent safety monitor.

  Full case reports for any patients requiring such monitoring should be submitted in the final study report. Patients with increases above the normal range in urine protein/creatinine ratios should be followed until there is resolution of this laboratory abnormality or to determine if the increases result in clinically relevant changes in renal function. Follow-up data should be submitted to the agency.

- ***Statistical information, including power of study and statistical assessments:***

  With a minimum of 150 patients randomized in a 1:1:1:1 ratio to the four treatment groups, power is greater than 90% to detect a treatment difference of at least 15% for each dose compared to placebo. The primary analysis population is the set of randomized patients with a baseline LDL-C and at least one post-baseline LDL-C. The primary endpoint will be analyzed using an analysis of covariance model including terms for treatment and other factors (e.g, center, gender or age) as appropriate with baseline LDL-C as a covariate.

  Changes in developmental measures (Tanner Stage and linear growth) will be summarized using descriptive statistics. Rates of new or worsening adverse events and laboratory safety outcomes will be summarized for all doses of rosuvastatin combined vs. placebo for the 12-week double blind period and for all patients treated in the extension phase.

- ***Labeling that may result from the study*:** 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. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.
- ***Timeframe for submitting reports of the study:*** Reports of the above studies must be submitted to the Agency on or before Dec. 31, 2009. 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.
- ***Response to Written Request:*** As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

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. 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 New Drug Application (NDA) or 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.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

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.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

If you have any questions, call Margaret Simoneau, M.S., R.Ph., Regulatory Project Manager, at 301-796-1295.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, 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/

Robert Meyer

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