DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-366

Astra Zeneca Pharmaceuticals LP, agent for
iPR Pharmaceuticals Inc.
Attention: Mark Eliason, M.Sc.
Director, Regulatory Affairs
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Eliason:

Please refer to your new drug application (NDA) dated June 26, 2001, received June 26, 2001, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crestor (rosuvastatin calcium) Tablets, 5 mg, 10 mg, 20 mg, and 40 mg.

We acknowledge receipt of your submissions dated June 7, July 1, August 1, September 9, and November 12, 2002, and January 23, February 12, March 13, April 15 and 17, May 8, 14 (2), 16, and 20, June 10 (2), 11, 12, 16, and 19, July 9, 18, 21, 22, 28, 29, and 31, and August 1, 4, and 12(2), 2003. The February 12, 2003, submission constituted a complete response to our May 31, 2002, action letter.

This new drug application provides for the use of Crestor (rosuvastatin calcium) Tablets for the following indications:

> As an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, non-HDL-C, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb).
>
> As an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV).
>
> To reduce LDL-C, total-C, and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted August 12, 2003) and the submitted labeling (immediate container and carton labels for the 5 mg, 10 mg, 20 mg, and 40 mg tablets submitted July 18, 2003). Marketing the products with FPL

that is not identical to the approved labeling may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-366**." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitment in your submission dated July 29, 2003. This commitment is listed below.

1. To perform an appropriately conducted pharmacokinetic study of Asians residing in the United States to further explore the pharmacokinetic differences that were previously found in Japanese residing in Japan and in Chinese residing in Singapore.

Protocol Submission:	November 13, 2003
Study Start:	August 13, 2004
Final Report Submission:	October 13, 2005

Submit clinical protocols to your IND for this product. Submit all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of this commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and number of patients entered into each study. All submissions, including supplements, relating to the postmarketing study commitment should be prominently labeled "**Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

We also refer to your submission of July 18, 2003, in which you describe the following distribution measures for marketing the 40-mg tablet in the United States which you have voluntarily undertaken. (b)(4) ---------- The 40-mg tablet will be made available only in a 30-count bottle to the retail market. At the time of the launch of CRESTOR, and after, -(b)(4)----------
(b)(4)----------
(b)(4)---------- These steps will help to ensure that the 40-mg dose is available only to patients who truly need this dose.

We further refer to your August 12, 2003, agreement to make 5 mg professional samples available for distribution within six months after approval of this NDA.

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third-party interveners have decided to appeal the

court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third-party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity, you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and
Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

Sufficient stability data have been submitted to support a 2-year expiry date.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Valerie Jimenez, Regulatory Project Manager at (301) 827-9090.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure
Package Insert

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
8/12/03 04:33:22 PM