DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-366/S-005

Astra Zeneca Pharmaceuticals LP
US Agent for IPR Pharmaceuticals, Inc.
Attention: Mark S. Eliason, MSc
Director, Regulatory Affairs
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Eliason:

Please refer to your supplemental new drug application dated November 15, 2004, received November 16, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crestor® (rosuvastatin calcium) Tablets.

We acknowledge receipt of your submissions dated January 7, 17, and 24, and February 2, 2005.

This supplemental new drug application provides for labeling changes in the following sections:

To the **CLINICAL PHARMACOLOGY,** *Special Populations*, *Race* subsection, after the first sentence, the paragraph was changed to read:

> However, pharmacokinetic studies, including one conducted in the US, have demonstrated an approximate 2-fold elevation in median exposure (AUC and C_{max}) in Asian subjects when compared with a Caucasian control group. (See WARNINGS, Myopathy/Rhabdomyolysis, PRECAUTIONS, General and DOSAGE AND ADMINISTRATION.)

To the **CLINICAL PHARMACOLOGY,** *Drug-Drug Interactions, Warfarin* subsection, the warfarin dose was changed from "20 mg" to "25 mg."

To the **WARNINGS,** *Myopathy/Rhabdomyolysis* subsection, the second paragraph, after the third sentence, was changed to read:

> In clinical trials, the incidence of myopathy and rhabdomyolysis increased at doses of rosuvastatin above the recommended dosage range (5 to 40 mg). In postmarketing experience, effects on skeletal muscle, e.g. uncomplicated myalgia, myopathy and, rarely, rhabdomyolysis have been reported in patients treated with HMG-CoA reductase inhibitors including rosuvastatin. As with other HMG-CoA reductase inhibitors, reports of rhabdomyolysis with rosuvastatin are rare, but higher at the highest marketed dose (40 mg). Factors that may predispose patients to myopathy with HMG-CoA reductase inhibitors include advanced age (≥65 years), hypothyroidism, and renal insufficiency.

To the **WARNINGS,** *Myopathy/Rhabdomyolysis* subsection, to the paragraph that begins with "Consequently" the following changes and renumbered were made:

1. "inadequately treated" was inserted before the word "hypothyroidism."

Additionally, a new item number 3 was inserted in the list to read:

3. The 40 mg dose of rosuvastatin is reserved only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose of rosuvastatin once daily (see DOSAGE AND ADMINISTRATION).

6. "dehydration" was added after the word "hypotension" to the list of examples.

To the **PRECAUTIONS,** *General* subsection, the third paragraph was changed to read:

> The result of a large pharmacokinetic study conducted in the US demonstrated an approximate 2-fold elevation in median exposure in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin) compared with a Caucasian control group. This increase should be considered when making rosuvastatin dosing decisions for Asian patients . (See WARNINGS, Myopathy/ Rhabdomyolysis; CLINICAL PHARMACOLOGY, Special Populations, Race, and DOSAGE AND ADMINISTRATION.)

To the **PRECAUTIONS,** *Pregnancy* subsection, third paragraph, the phrase "In pregnant rats given oral gavage doses of 2, 20, 50 mg/kg/day" was changed to ". . . 2, 10, 50 mg/kg/day."

To the **ADVERSE REACTIONS,** *Clinical Adverse Experiences*, *Laboratory Abnormalities* subsection, second paragraph, "creatinine" was changed to "creatine."

To the **ADVERSE REACTIONS** section, a new "*Postmarketing Experience"* subsection was added:

> **Postmarketing Experience**
> In addition to the events reported above, as with other drugs in this class, the following event has been reported during postmarketing experience with CRESTOR, regardless of causality assessment: very rare cases of jaundice.

To the **DOSAGE AND ADMINISTRATION,** *Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Type IIa and IIb)* subsection, the paragraph <u>after the third sentence</u> was changed and a second, bolded paragraph was added as follows:

> However, initiation of therapy with 5 mg once daily should be considered for patients requiring less aggressive LDL-C reductions, who have predisposing factors for myopathy, and as noted below for special populations such as patients taking cyclosporine, Asian patients, and patients with severe renal insufficiency (see CLINICAL PHARMACOLOGY, Race, and Renal Insufficiency, and Drug Interactions. For patients with marked hypercholesterolemia (LDL-C > 190 mg/dL) and aggressive lipid targets, a 20-mg starting dose may be considered. After initiation and/or upon titration of CRESTOR, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

The 40-mg dose of CRESTOR is reserved only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose of CRESTOR once daily (see WARNINGS, Myopathy/Rhabdomyolysis). When initiating statin therapy or switching from another statin therapy, the appropriate CRESTOR starting dose should first be utilized, and only then titrated according to the patient's individualized goal of therapy.

To the **DOSAGE AND ADMINISTRATION** section, a new "*Dosage in Asian Patients"* subsection has been added to read:

Dosage in Asian Patients
Initiation of CRESTOR therapy with 5 mg once daily should be considered for Asian patients. The potential for increased systemic exposures relative to Caucasians is relevant when considering escalation of dose in cases where hypercholesterolemia is not adequately controlled at doses of 5, 10, or 20 mg once daily. (See WARNINGS, Myopathy/ Rhabdomyolysis, CLINICAL PHARMACOLOGY, Special Populations, Race, and PRECAUTIONS, General).

The **HOW SUPPLIED** section has been changed to reflect debossing changes made to the 5, 10, 20, and 40 mg tablets. The debossing now consists of the word "Crestor" and the mg strength of the tablet on one side of the tablet; the other side of the tablet is blank.

We completed our review of this application, as amended. This application 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 January 24, 2005).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. For administrative purposes, designate this submission "**FPL for approved supplement NDA 21-366/S-005**." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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

If you have any questions, call Margaret Simoneau, M.S., R.Ph., Regulatory Project Manager, at (301) 827- 6411.

Sincerely,

{See appended electronic signature page}

David G. Orloff, MD
Director
Division of Metabolic & Endocrine Drug Products
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/

David Orloff

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