

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-366

Approval Letter(s)



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.

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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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-366

Approvable Letter (S)



NDA 21-366

5/31/02

AstraZeneca Pharmaceuticals LP, agent for
iPR Pharmaceuticals Inc.
Attention: Mark S. Eliason
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 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crestor (rosuvastatin calcium) Tablets, 10 mg, 20 mg, 40 mg, 80 mg.

We acknowledge receipt of your submissions dated June 29, July 2, August 9, 17, and 23, October 8, 22, 24, and 30, November 2 and 8, and December 6, 2001, and January 23, February 7, 13, 18, and 21, March 14, April 4 and 23, and May 10 and 22, 2002.

We have completed the review of this application, as amended, and find that the proposed 80-mg dose is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The application presented consistent evidence of little added benefit of the 80-mg dose over the 40-mg dose, even in patients with homozygous familial hypercholesterolemia. This small benefit does not outweigh the risks of myopathy and renal toxicity apparent at this dose.

The 10-mg, 20-mg, and 40-mg proposed doses are approvable. Before this application may be approved, however, it will be necessary for you to address the following:

CLINICAL

1. The safety database in the NDA does not allow a complete assessment of the risk-benefit profile of rosuvastatin.

- a. The numbers of patients exposed long term to rosuvastatin are inadequate to provide assurance of the safety of either the 20-mg or the 40-mg proposed dose. Additional safety information is needed to permit conclusions regarding the drug's therapeutic index, given the high incidence of rhabdomyolysis seen at the 80-mg dose. You must establish that the risk of myotoxicity, normalized for effectiveness at lowering LDL-C, does not exceed that of other drugs in the HMG CoA-reductase inhibitor class. We also note non-statistically significant numeric differences between drug- and placebo-treated groups in the incidence of categorical CK elevations among the small numbers of non-Caucasians in the clinical trials submitted to the NDA. You should include larger numbers of racial and ethnic minority patients in subsequent trials of rosuvastatin. Be advised that patients who were previously taking 80 mg of rosuvastatin in clinical trials or their extension phases, but who are now taking 40 mg per day, will not be considered in the required additional assessment of the safety of the 40-mg dose. This is because it is presumed that those susceptible to the myotoxic effects of the drug have already been culled from the randomized cohort.
 - b. Safety monitoring in the clinical trials completed to date was not adequate to determine the nature, magnitude, and frequency of renal adverse events observed in patients treated with rosuvastatin, nor whether nephrotoxicity is reversible, chronic, or progressive. You must address why the risk of rosuvastatin nephrotoxicity does not outweigh the benefit of the drug given the numerous alternative products available. Additional studies across the full range of proposed rosuvastatin doses and in relevant clinical subgroups (e.g., diabetics, hypertensives) are needed to address this safety concern.
 - c. Given the unresolved concern of the possible increased myotoxicity of rosuvastatin and the documented interaction with gemfibrozil, the risk of adverse events (i.e., myopathy) due to rosuvastatin over a range of doses when used in combination with gemfibrozil must be further addressed in clinical studies. These studies should include assessments of rosuvastatin plasma levels.
2. Our review of the pivotal clinical trials finds the data are inadequate to assess optimal dosing for rosuvastatin. We believe that doses below those proposed for marketing have potential clinical utility. In light of the unresolved safety concerns with this drug, discussed in (1), above, the safe use of rosuvastatin may require the availability of lower dosage strengths (e.g., for patients treated with gemfibrozil or cyclosporin, for those with renal impairment, or the elderly).

BIOPHARMACEUTICS

3. The mean exposure parameters (C_{max} and AUC) were similar in normal volunteers and patients with mild-to-moderate renal insufficiency. However, there was significant variability and a bimodal distribution in the exposure data from the patients with mild renal insufficiency, and there were too few patients with moderate renal insufficiency to support the conclusion of no safety concerns in patients with mild-to-moderate renal impairment. Further clinical data are needed to support this conclusion. This is particularly of concern given the fact that one of the major risk factors for rhabdomyolysis in the clinical trials was baseline renal insufficiency.

4. The dissolution method and specification should be modified as follows:

- Dissolution test conditions
 - Medium: _____
 - Apparatus: _____
 - Volume: _____
 - Temperature: _____
 - Sampling times: _____
- Dissolution specification
 - Q = _____% at 30 minutes

CHEMISTRY, MANUFACTURING, AND CONTROLS

5. Provide _____ test to be performed upon receipt of drug substance intermediates when they are shipped from one facility to another. Indicate how long and under what conditions the intermediates are stored before they are shipped, after they are received, and before they are used in the next step of the manufacture of drug substance.

6. Establish microbial limits for the drug substance, or show that it is not capable of supporting microbial growth or viability.

7. Provide _____ by _____ in _____ "complies with approved test" for _____ for the drug product.

8. _____
_____ Provide the actual data from stability studies on 20 batches for review.

9. Submit an agreement to report stability data for at least one commercial batch of each strength, or at least the strengths to represent the different formulations, of the drug product in the first annual report.

10. As discussed in (2) above, our review of data addressing the efficacy of doses below 10 mg supports clinically significant LDL-C-lowering effects. Should you propose to market these doses in the future, appropriate information addressing Chemistry, Manufacturing, and Controls would be required.

LABELING

11. Comments regarding labeling are deferred pending resolution of the issues described above.

ADMINISTRATIVE

12. The financial disclosure forms (forms FDA 3454 and 3455) are signed by an official of _____ . These forms must be resubmitted with the signature of the chief financial officer or another responsible corporate official or representative of iPR Pharmaceuticals, Inc.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that any complete response to this letter include all safety information you have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110 (for the approvable proposed doses) and 314.120 (for the not-approvable dose). In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with the Division of Metabolic and Endocrine Drug Products to discuss what further steps need to be taken before the application may be approved.

In addition, we provide the following comments from the review team. These issues do not need to be resolved before the NDA can be approved:

Biopharmaceutics:

- A. We recommend that the rosuvastatin concentration and response measures (LDL-C, HDL-C, etc.) be determined at trough time points (i.e., time just before next dose) in future clinical trials for further analyses on exposure-response relationship for efficacy and/or toxicity assessment.

Chemistry, Manufacturing, and Controls:

- B. Provide an _____
_____ section of the NDA submission. Also provide an _____ of the ZD4522 lactone that supports the tabular data.
- C. Provide a brief description of the sampling plan for the drug product.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call William C. Koch, R.Ph., Regulatory Project Manager, at (301) 827-6412.

Sincerely,

{See appended electronic signature page}

Sandra L. Kweder, M.D.
Acting 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/

Sandra L. Kweder
5/31/02 03:55:42 PM

NDA 21-366

Crestor (rosuvastatin calcium) tablets, 10 mg, 20 mg, 40 mg, 80 mg

The preceding Action Letter has been reviewed by the undersigned:

Name	Discipline	Signature	Recommended Action	Date
W. Lubas, M.D.	Medical Officer			
M. H. Parks, M.D.	Medical Team Leader			
J. Gong, Ph.D.	Pharmacology Reviewer			
K. Davis-Bruno, Ph.D.	Pharmacology Team Leader			
S. Kelly, Ph.D.	Chemist			
S. K. Moore, Ph.D.	Chemistry Team Leader I			
S. Chung, Ph.D.	Biopharmaceutics			
H. Ahn, Ph.D.	Biopharmaceutics Team Leader			
J. Mele, M.S.	Statistician	<i>lets re-review</i> IS	<i>the letter needs work</i>	5/29/02
T. Sahlroot, Ph.D.	Biometrics 2 Team Leader			
E. Galliers	Chief, Project Mgt. Staff	<i>4/1/02</i> IS	—	4/30/02
D. G. Orloff, M.D.	Division Director	IS	RE	5/3/02

157 pages redacted from this section of
the approval package consisted of draft labeling