CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-366

Correspondence

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 20 2002

Barbara K. Zedler, M.D.
National Clinical Research
2809 Emerywood Parkway, Suite 140
Richmond, Virginia 23294

Dear Dr. Zedler:

Between January 14 and 25, 2002, Ms. Candice J. Cortes, representing the Food and Drug Administration (FDA), met with you and members of your staff, to review your conduct of three clinical studies (protocols #4522IL/0024, #4522IL/0028, and #4522IL/0034) of the investigational drug Crestor™ (rosuvastatin calcium), performed for AstraZeneca. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that, except for the problem with maintaining constant temperature for the study drug, you did adhere to pertinent federal regulations governing your conduct of clinical investigations.

We note in your letter of January 30, 2002, in response to the Form FDA 483, that National Clinical Research has moved to a new facility, and the problems with temperature control appear to have been corrected.

We appreciate the cooperation shown Investigator Cortes during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact Khin Maung U, M.D., Branch Chief, Good Clinical Practice I, by letter at the address given below.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003561753
Field Classification: VAI
Headquarters Classification:
_____1)NAI
__X _2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiencies noted:
____inadequate informed consent
____inadequate drug accountability
_X_ failure to adhere to protocol
____inadequate records
____failure to report ADRS
____other
Deficiency Code: 5

cc:
HFA-224
HFD-510 Doc.Rm. NDA# 21-366
HFD-510 Review Div.Dir.(Orloff)
HFD-510 MO (Lubas)
HFD-510 PM (Koch)
HFD-46/47 GCP File # 10567
HFD-47 CSO (Currier)
HFD-47 Reviewer (Blay)
HFR-CE250 DIB (Wagner)
HFR-CE250 Bimo Monitor (Salisbury)
HFR-CE2545 Field Investigator (Cortes)

r/d:CAC:2/28/02
reviewed:AEH:**(3/1/02)**
REVISED: RAB: 3/4/02
f/t:mb:**(3/6/02)**
o:\cac:\zedler.doc

Reviewer Note to Rev. Div. M.O.

This inspection covered 3 protocols for Crestor, NDA 21-366. For protocol #0024, 14 subjects were enrolled and 5 subjects' records were reviewed. For protocol #0028, 37 subjects were enrolled and 7 records were reviewed. For protocol 0034, 85 subjects were enrolled and 10 subjects' records were reviewed. The field investigator reviewed the data on source documents, case report forms, and line listings submitted by the sponsor and found no discrepancies. All subjects had a diagnosis of hypercholesterolemia prior to entry into the study. All concomitant therapy appeared to have been accurately reported and AEs were reported in the CRFs. The only problem noted on the FDA Form 483 was that the temperature of the drug storage room was out of the range specified by the protocol; (but often by and not on consecutive days). Unless this drug is EXTREMELY sensitive to temperature change, this protocol violation should not affect the drug, and the data reviewed during the inspection would be acceptable to use in support of an approval decision for NDA 21-366.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Leonard Keilson, M.D., M.P.H.
Maine Medical Center
Center for Lipids & Cardiovascular Health
48 Gilman Street
Portland, Maine 04102

MAR - 7 2002

Dear Dr. Keilson:

Between January 22 and 25, 2002, Ms. Lori A. Holmquist, representing the Food and Drug Administration (FDA), met with you to review your conduct of clinical studies (Trial Number 4522IL/0031), and (Trial Number 4522IL/0034) of the investigational drug Crestor™, performed for AstraZeneca Pharmaceuticals, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did adhere to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Holmquist during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact Khin Maung U, M.D., Branch Chief, Good Clinical Practice I, by letter at the address given below.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI:3003520889
Field Classification: NAI
Headquarters Classification:
__X__1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

cc:
HFA-224
HFD-580 Doc.Rm. NDA# 21-366
HFD- 580 Review Div.Dir.
HFD- 580 MO (Lubas)
HFD- 580 PM (Koch)
HFD-45 Reading File
HFD-47 Chron File
HFD-47 GCP File # 010553
HFD-47 GCP Reviewer (Blay)
HFD-47 CSO (Currier)
HFR- NE250 DIB (Kravchuk)
HFR- NE250 Bimo Monitor (Madigan)
HFR- NE2500 Field Investigator (Holmquist)
r/d:CAC:2/15/02
revised:2/26/02
reviewed:AEH:2/28/02
f/t:sg:3/1/02
o:\cac:\keilson.doc

Reviewer Note to Rev. Div. M.O.

Sixteen of 16 subject records were examined for Protocol 0031. Ten of 21 subject records were examined for Protocol 0034. No problems were found and no FDA Form 483 was issued at the conclusion of the inspection. There were no discrepancies noted that would invalidate the data submitted in support of NDA 21-366.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Jeffrey T. Whitmer, M.D., Ph.D.
Evan A. Stein, M.D., Ph.D.
Metabolic Atherosclerosis Research Center
2350 Auburn Avenue
Cincinnati, Ohio 45219

Dear Drs. Whitmer and Stein:

Between January 15 and 22, 2002, Mr. Joseph X. Kaufman, representing the Food and Drug Administration (FDA), met with you to review the conduct of clinical studies (protocols #4522IL/0033 and 0035 by Dr. Whitmer as principal investigator and protocol 4522IL/0034 by Dr. Stein as principal investigator) of the investigational drug Crestor® (rosuvastatin), performed for AstraZeneca Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Kaufman during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact Khin Maung U, M.D., Branch Chief, Good Clinical Practice I, by letter at the address given below.

Sincerely yours,

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 1527456
Field Classification: NAI
Headquarters Classification:
__X _1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

cc:
HFA-224
HFD-510 Doc.Rm. NDA 21-366
HFD-510 Review Div.Dir. Orloff
HFD-510 MO Lubas
HFD-510 PM Koch
HFD-45 Reading File
HFD-47 c/r/s GCP File #3872
HFD-47 Blay/Hajarian
HFR-CE450 DIB/ Heppe
HFR-CE450 BIMO/Eastham
HFR-CE450 Field Investigator/Kaufman

r/d:GRH:2/8/02

O:\GRH\WHITMER-STEIN NAI.DOC

Reviewer Note to Rev. Div. M.O.,

Protocol 4522IL/0033
Of 56 subjects screened, 39 subjects were randomized and 38 subjects completed the study. One subject withdrew due to nausea. The records of 7 subjects were reviewed in depth. No deviations were noted. No Form FDA 483 was issued. The data appeared acceptable.

Protocol 4522IL/0035
Of 37 subjects screened, 19 subjects were randomized and all 19 subjects completed the study. The records of 6 subjects were reviewed in depth. No deviations were noted. No Form FDA 483 was issued. The data appeared acceptable.

Protocol 4522IL/0034: "An Open-Label, Multinational, Multicenter, **Extension** Trial to Assess the Long-Term Safety and Efficacy of ZD4522 in Subjects in the ZD4522 Clinical Trial Program"

Of 211 subjects consented, 202 subjects are currently active. Nine subjects withdrew/terminated from the study. The 36 SAEs were reported accurately in the date comparison between the subjects' case report forms and the data the sponsor provided to FDA. The records of 8 subjects were reviewed in depth. No deviations were noted. No Form FDA 483 was issued. The data appeared acceptable.

Redacted 11

pages of trade

secret and/or

confidential

commercial

information

AstraZeneca

May 16, 2001

Dr. David G. Orloff, Division Director
Division of Metabolism and Endocrine Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-No. 510, Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

Re: CRESTOR™ (rosuvastatin calcium) tablets
NDA 21-366

Dear Dr. Orloff:

iPR Pharmaceuticals, Inc. hereby authorizes AstraZeneca Pharmaceuticals LP to serve as its agent for submitting and executing all matters relating to CRESTOR™ (rosuvastatin calcium) tablets

Yours faithfully,
For and on behalf of
iPR Pharmaceuticals, Inc.

Rubén Freyre
President and General Manager

iPRPharmaceuticals, Inc.
A Part of AstraZeneca PLC

PO Box 1967
Carolina PR 00984-1967

Tel 787 750 5353
Fax 787 750 5332

AstraZeneca

Date: July 22, 2003

Center for Drug Evaluation and Research
Food and Drug Administration
FDR/Room 8B45
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-366
CRESTOR® (rosuvastatin calcium) Tablets
Response to Requests for Phase 4 Commitment

Dear Madam/Sir:

Reference is made to the teleconference held with Division NDA Review Team members on July 21, 2003 regarding Phase 4 study commitments. For this commitment the Division proposes that AstraZeneca Pharmaceuticals LP (AstraZeneca) perform "an appropriately conducted PK study of Asians residing in the United States to explore the PK differences observed in Japanese residing in Japan and Chinese residing in Singapore".

With this letter, AstraZeneca hereby commits to performing the above study request. In meeting this request, AstraZeneca commits to the following timelines:

1. Submission of the proposed study protocol will occur within 3 months from the date of the NDA Approval Letter,
2. The initiation of the proposed study would occur within 12 months from the date of the NDA Approval Letter
3. A final clinical trial report would be submitted to the NDA within 26 months from the date of the NDA Approval Letter.

As discussed in the referenced teleconference, it is the expectation of both parties that provided the outcome of the proposed PK study demonstrates no marked differences between the comparison groups, the labeling for CRESTOR® will be amended to reflect this outcome. It is also the understanding of both parties that if the outcome does not address the original intentions of the proposed study, additional studies may be necessary.

7-22-03

US Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

The confidentiality of this submission, and all information contained herein, is claimed by AstraZeneca under all applicable laws and regulations. Disclosure of any such information is not authorized without the prior written authorization of AstraZeneca.

If you should have any questions or requests for additional information regarding this NDA please address them to me, or in my absence, to Mr. Aaron Packman, (302) 885-1808.

Sincerely,

Mark S. Eliason, Director
Regulatory Affairs
Telephone: (302) 885-5294
Fax: (302) 885-5334
Mobile: (302) 897-8087

MSE/giw
Enclosures

Desk Copy: Margaret Simoneau, R. Ph., HFD-510, Room 14B-04

Memo to File

NDA #:	21-366
Sponsor:	AstraZeneca
Drug:	Crestor (rosuvastatin calcium)
Memo Date:	15-Jul-03
Office/Division:	OCPB / DPE–2
Reviewer:	Sang M. Chung, Ph.D.
Team Leader:	Hae-Young Ahn, Ph.D.
Issue:	Recommendation of a Phase IV Study

The original NDA reported approximately a 2-fold rosuvastatin exposure elevation in Japanese residing in Japan compared to Caucasian subjects. Safety of rosuvastatin has not been fully evaluated in subjects of Asian ethnicity residing in U.S.A. compared to that in Caucasian subjects.

Therefore, the Agency recommends a Phase IV study as follow:

- A single dose pharmacokinetic study in subjects of Asian ethnicity residing in U.S.A. and comparing the results to those in historical Caucasian subjects.

AstraZeneca

TIME SENSITIVE PATENT INFORMATION

Date: August 4, 2003

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

RECEIVED
AUG 0 8 2003
CDR/CDER

Central Document Room (HFD-94)
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

Re: NDA 21-366
CRESTOR® (rosuvastatin calcium) Tablets
Amendment to Patent Information

Dear Madam/Sir:

We take this opportunity to amend the patient information submitted to NDA 21-366 for CRESTOR® (rosuvastatin calcium) Tablets. A new patent was granted on July 8, 2003 (US Patent No. 6,589,959) which covers the formulation, composition, and/or method of use of CRESTOR®. Accordingly, information relative to this patent is now being submitted.

The confidentiality of this submission, and all information contained herein, is claimed by AstraZeneca under all applicable laws and regulations. Disclosure of any such information is not authorized without the prior written authorization of AstraZeneca.

If you should have any questions or requests for additional information regarding this NDA please address them to me, or in my absence, to Mr. Aaron Packman, (302) 885-1808.

Sincerely,

Mark S. Eliason, Director
Regulatory Affairs
Telephone: (302) 885-5294
Fax: (302) 885-5334
Mobile: (302) 897-8087

MSE/giw

Desk Copy: Valerie Jimenez, R. Ph., HFD-510, Room 14B45

US Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

X09 (8/00)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
IPR Pharmaceuticals, Inc.	
TELEPHONE NO. *(Include Area Code)* (800) 456-3669	FACSIMILE (FAX) Number *(Include Area Code)* (302) 886-2822
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* P.O. Box 1967 Carolina, PR 00984-1967	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE: AstraZeneca Pharmaceuticals LP Mark S. Eliason, M.Sc. Regulatory Affairs Director 1800 Concord Pike P.O. Box 8355 Wilmington, DE 19803-8355 (302) 885-5294 (302) 885-5334

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-366

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
rosuvastatin calcium	CRESTOR® (rosuvastatin calcium) tablets

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(if any)*
Bis [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt	S4522, ZD4522

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	5mg, 10mg, 20mg, 40mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
CRESTOR® is indicated: as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-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); an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson ——— IV); to reduce LDL-C, TC, and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) or if such treatments are unavailable

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER Patent Information

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
General Correspondence: Patent Information

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS: ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
IND 56,385; NDA 21-366; DMFs

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d) (1), 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50 (e) (2) (i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d) (2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d) (3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d) (4))
☐	8. Clinical data section (e.g., 21 CFR 314.50 (d) (5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50 (d) (5) (vi) (b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50 (d) (6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50 (f) (1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f) (2); 21 CFR 601.2)
☒	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k) (1))
☐	17. Field copy certification (21 CFR 314.50 (l) (3))
☐	18. Use Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Mark S. Eliason	Mark S. Eliason, M.Sc. Regulatory Affairs Director	August 4, 2003

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
1800 Concord Pike P.O. Box 8355 Wilmington, DE 19803-8355	(302) 885-5294

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

AstraZeneca

Date: July 21, 2003

Center for Drug Evaluation and Research
Food and Drug Administration
FDR/Room 8B45
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-366
CRESTOR® (rosuvastatin calcium) Tablets
Response to Requests for Additional Information
Amended Patent Information

Dear Madam/Sir:

The information contained in this submission is the official response to a July 21, 2003 request from the Division for amended patent information for CRESTOR®. This information has been informally submitted previously to the Division via fax.

The confidentiality of this submission, and all information contained herein, is claimed by AstraZeneca Pharmaceuticals LP (AstraZeneca) under all applicable laws and regulations. Disclosure of any such information is not authorized without the prior written authorization of AstraZeneca.

If you should have any questions or requests for additional information regarding this NDA please address them to me, or in my absence, to Mr. Aaron Packman, (302) 885-1808.

Sincerely,

Mark S. Eliason, Director
Regulatory Affairs
Telephone: (302) 885-5294
Fax: (302) 885-5334
Mobile: (302) 897-8087

MSE/giw
Enclosures

Desk Copy: Margaret Simoneau, R. Ph., HFD-510, Room 14B-04

US Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT IPR Pharmaceuticals, Inc.	DATE OF SUBMISSION July 21, 2003
TELEPHONE NO. *(Include Area Code)* (800) 456-3669	FACSIMILE (FAX) Number *(Include Area Code)* (302) 886-2822
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* P.O. Box 1967 Carolina, PR 00984-1967	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE: AstraZeneca Pharmaceuticals LP Mark S. Eliason, M.Sc. Regulatory Affairs Director 1800 Concord Pike P.O. Box 8355 Wilmington, DE 19803-8355 (302) 885-5294 (302) 885-5334

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-366

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* rosuvastatin calcium	PROPRIETARY NAME *(trade name)* IF ANY CRESTOR® (rosuvastatin calcium) tablets
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* Bis [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt	CODE NAME *(If any)* S4522, ZD4522

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	5mg, 10mg, 20mg, 40mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
CRESTOR® is indicated: as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, —— TG levels and to increase HDL-C anc in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb); an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson —— IV); to reduce LDL-C, TC, and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) or if such treatments are unavailable

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER Amended Patent Information

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Amended Patent Information

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 | THIS APPLICATION IS: ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
IND 56,385; NDA 21-366; DMFs ——

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d) (1), 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50 (e) (2) (i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d) (2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d) (3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d) (4))
☐	8. Clinical data section (e.g., 21 CFR 314.50 (d) (5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50 (d) (5) (vi) (b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50 (d) (6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50 (f) (1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f) (2); 21 CFR 601.2)
☒	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k) (1))
☐	17. Field copy certification (21 CFR 314.50 (l) (3))
☐	18. Use Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Mark S. Eliason	Mark S. Eliason, M.Sc. Regulatory Affairs Director	July 21, 2003

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
1800 Concord Pike P.O. Box 8355 Wilmington, DE 19803-8355	(302) 885-5294

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

04.23.03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-366

INFORMATION REQUEST LETTER

Astra Zeneca LP
Attention: Mark Eliason
Director, Regulatory Affairs
U.S. Agent for IRP Pharmaceuticals, Inc.
1800 Concord Pike, PO BOX 8355
Wilmington, DE 19803-8355

Dear Mr. Eliason:

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

We also refer to the teleconference on February 26, 2003, held with the Division and representatives from your firm, during which your were requested to submit a proposal detailing how the ex-USA post-marketing safety reports, along with corresponding prescription information, would be submitted to the pending application. This letter serves to formally request this information.

We also refer to your March 13, 2003, submission containing your proposal to submit specific information, based on a 4-week collection period, to the pending NDA. We find your proposal acceptable.

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

Sincerely,

/S/

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
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/

Valerie Jimenez
4/23/03 09:50:20 AM
Signing for David G. Orloff, M.D.

03/03/03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-366

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

Dear Mr. Eliason:

We acknowledge receipt on February 12, 2003 of your February 12, 2003 resubmission to your new drug application for CRESTOR® (rosuvastatin calcium) Tablets.

We consider this a complete, class 2 response to our May 31, 2002 action letter. Therefore, the user fee goal date is August 12, 2003.

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

Sincerely,

/S/

{See appended electronic signature page}

Valerie Jimenez
Regulatory Project Manager
Division of Metabolic & Endocrine Drug Products
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/

Valerie Jimenez
3/3/03 11:59:27 AM

01.02.02

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-366

AstraZeneca Pharmaceuticals LP
Attention: Mark S. Eliason, M.Sc.
Director, Regulatory Affiars
1800 Concord Pike, PO Box 8355
Wilmington, Delaware 19850-8355

Dear Mr. Eliason:

Please refer to the meeting between representatives of your firm and FDA on November 1, 2001. The purpose of the meeting was to discuss drug-drug interaction study with gemfibrozil requested by the Division.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-6412.

Sincerely,

/S/

{See appended electronic signature page}

William C. Koch, R.Ph.
Regulatory Project Manager
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-366

INFORMATION REQUEST LETTER

10/23/01

AstraZeneca Pharmaceuticals LP
Attention: Mark S. Eliason, M.Sc.
Director, Regulatory Affairs
1800 Concord Pike, PO Box 8355
Wilmington, Delaware 19850-8355

Dear Mr. Eliason:

Please refer to your June 26, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crestor (rosuvastatin calcium) Tablets.

We are reviewing the safety data submitted to your submission and have the following request from the Biopharmaceutics reviewer.

> Complete a single-dose pharmacokinetic (PK) study of rosuvastatin calcium administered to subjects treated to steady state with the highest approved dose of gemfibrozil (1200 mg/day). Please submit a protocol for our review prior to initiation of the study.

Subsequent to the voluntary withdrawal of a previously approved HMG CoA reductase inhibitor for safety reasons, the Division is re-evaluating its requirements for marketing approval of new molecular entities in this class. Data from the above requested PK study would contribute significantly to the ability of the Division to assess the safety of Crestor (rosuvastatin calcium) Tablets for the proposed indications within this review cycle.

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

Sincerely,

/S/

David G. Orloff, M.D.
Director
Division of Metabolic
and Endocrine Drug Products, HFD-510
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/

David Orloff
10/23/01 11:04:33 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-366

INFORMATION REQUEST LETTER

AstraZeneca Pharmaceuticals LP
Attention: Mark S. Eliason, M.Sc.
Director, Regulatory Affairs
1800 Concord Pike, PO Box 8355
Wilmington, Delaware 19850-8355

9/28/01

Dear Mr. Eliason:

Please refer to your June 26, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crestor (rosuvastatin calcium) Tablets.

We are reviewing the Pharmacology/Toxicology section of your submission and have the following comments and information request from the statistical reviewer. We request a prompt written response in order to continue our evaluation of your NDA.

In the rat study (TCR2852), a slight inconsistency in the tumor incidences or names under HAEM/LYMPH/RETIC organ type was found between the neoplastic incidence summary table (Appendix J7) and the electronic data file (tumor.xpt). The tumor names and incidences presented in the Tumor Statistics section, however, match the names and incidences generated from the electronic data file (tumor.xpt).

The male rats in the neoplastic incidence table, under HAEM/LYMPH/RETIC, show

Group	1	2	3	4	5	6
Malignant Lymphoma	2	1	1	0	2	2

However, the electronic data file (tumor.xpt) shows

Group	1	2	3	4	5	6
Malignant Lymphoma-Pleomorphic	0	0	0	0	2	0
Lymphocytic Leukaemia	2	1	1	0	0	2

Likewise, the females in the neoplastic incidence table show

Group	1	2	3	4	5	6
Malignant Lymphoma	1	0	1	0	3	0

The electronic data file (tumor.xpt), however, shows

Group	1	2	3	4	5	6
Malignant Lymphoma-Lymphocytic	0	0	0	0	1	0
Lymphocytic Leukemia	1	0	1	0	2	0

The reviewer suspects that malignant lymphoma is a combined form of pleomorphic lymphoma, lymphocytic lymphoma, and/or lymphocytic leukemia. Although this discrepancy will not cause any delay in the review process, it will be helpful to the reviewer's understanding of the submitted data if this issue can be clarified.

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

Sincerely,

/S/

Todd Sahlroot, Ph.D.
Team Leader, Biometrics II for the
Division of Metabolic
and Endocrine Drug Products, HFD-510
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/

Todd Sahlroot
9/28/01 09:59:48 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-366

6/29/01

AstraZeneca Pharmaceuticals LP, agent for
iPR Pharmaceuticals Inc.
Attention: Mark S. Eliason
Director, Regulatory Affairs
1800 Concord Pike, PO Box 8355
Wilmington, DE 19803-8355

Dear Mr. Eliason:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Crestor (rosuvastatin calcium) Tablets, 10, 20, 40, 80 mg

Name of Applicant: iPR Pharmaceuticals Inc.

Review Priority Classification: Standard (S)

Date of Application: June 26, 2001

Date of Receipt: June 26, 2001

Our Reference Number: NDA 21-366

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 25, 2001, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be April 26, 2001, and the secondary user fee goal date will be June 26, 2001.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6412.

Sincerely,

{See appended electronic signature page}

William C. Koch, R.Ph.
Regulatory Project Manager
Division of Metabolic
and Endocrine Drug Products, HFD-510
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/

William Koch
6/29/01 05:20:15 PM

Redacted 2

pages of trade

secret and/or

confidential

commercial

information