CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-366/S-016

OTHER REVIEW(S)

Division of Metabolism & Endocrine Products

Labeling Review

Application Number: NDA 21-366/S-016

Name of Drug: Crestor (rosuvastatin) Tablets

Sponsor: AstraZeneca

Submission Date: April 7, 2009, and January 29, 2010 (email) label

Background and Summary:

Crestor is indicated:

1. 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);

2. as an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV);

3. 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.

4. slowing of the progression of atherosclerosis

It is supplied in the tablet dose strengths of 5, 10, 20, and 40 mg.

Supplement S-018 was the last approved Package Insert (PI) which provided for changes to the **DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS,** and **CLINICAL PHARMACOLOGY** sections of the Crestor package insert to add additional information on protease inhibitors.

Supplement S-016, a SE-1 efficacy supplement, provides for a new indication for CRESTOR for the primary prevention of cardiovascular disease, based on the results of Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER).

Review:

Addition of the following information:

5 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Conclusion:

The PI/PPI submitted on January 29, 2010 (by email) was deemed acceptable by the reviewing team (Eric Colman, Amy Egan, Mary Roberts, Todd Sahlroot and David Hoberman). Agency will issue an approval letter on this prior approval labeling supplement.

Reviewed by: M.A. Simoneau, R.Ph., Regulatory Project Manager/2.4.10

POST LABEL REVIEW NOTES

The label review was completed using the MSWord version sent by the sponsor and accepted by the review team on January 29, 2010 (by email). This PI and PPI were converted to a PDF document and attached to the approval letter. When the approval letter was signed, it was noted that in section **12.3 Pharmacokinetics, Race,** six lines were missing:

> Black or Afro-Caribbean groups. 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.

The approval letter was re-issued on Tuesday, February 9, 2010, with the text included. The text was deleted inadvertently during the MSWord conversion to a PDF document due to an imbedded formatting change from October 29, 2007 (6:09 pm) in the MSWord version that was sent by the sponsor on January 29, 2010 (by email).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21366	SUPPL-16	IPR PHARMACEUTICALS INC	CRESTOR(ROSUVASTATIN CALCIUM)10/20/40/80

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARGARET A SIMONEAU
02/18/2010

42 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

35 Page(s) Withheld

____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

____ Draft Labeling (b5)

____ Deliberative Process (b5)

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-366 Supplement # 016 Efficacy Supplement Type SE- 1

Proprietary Name: Crestor
Established Name: rosuvastatin calcium tablets
Strengths: 5, 10, 20 and 40mg

Applicant: IPR Pharmaceuticals, Inc
Agent for Applicant (if applicable): Astra Zeneca Pharmaceuticals LP

Date of Application: April 8, 2009
Date of Receipt: April 8, 2009
Date clock started after UN: NA
Date of Filing Meeting: May 27, 2009
Filing Date: June 7, 2009
Action Goal Date (optional): User Fee Goal Date: February 8, 2010

Indication(s) requested: In adult patients with an increased risk of cardiovascular disease based on the presence of cardiovascular disease risk markers such as an elevated hsCRP level, age, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, CRESTOR is indicated to:

- reduce the risk of total mortality
- reduce the risk of cardiovascular death
- reduce the risk of stroke
- reduce the risk of myocardial infarction
- reduce the risk of arterial revascularization
- reduce the risk of unstable angina

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☒ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the*

User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☒ NO ☐
  If yes, explain: NDA 21-366 original

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

  1. This application is a paper NDA YES ☐

  2. This application is an eNDA or combined paper + eNDA YES ☐
     This application is: All electronic ☐ Combined paper + eNDA ☐
     This application is in: NDA format ☐ CTD format ☐
     Combined NDA and CTD formats ☐

     Does the eNDA, follow the guidance?
     (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☐ NO ☐

     If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format? Gateway submission/Mod

Additional comments:

3. This application is an eCTD NDA. YES ☒
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐
- Exclusivity requested? YES, 3 Years NO ☐
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES ☒ NO ☐
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐
- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☐ NO ☐
- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 56,385

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) NA/Comments sent 10.6 and 14.09 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) NA NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☐ NO ☒

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☐ NO ☒

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☒ YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? NA YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☒

Chemistry

• Did applicant request categorical exclusion for environmental assessment?	YES ☒	NO ☐
If no, did applicant submit a complete environmental assessment?	YES ☐	NO ☐
If EA submitted, consulted to EA officer, OPS?	YES ☐	NO ☒
• Establishment Evaluation Request (EER) submitted to DMPQ?	YES ☐	NO ☐
• If a parenteral product, consulted to Microbiology Team?	YES ☐	NO ☒

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 27, 2009

NDA #: 21-366/S-016

DRUG NAMES: Crestor (rosuvastatin calcium)

APPLICANT: AstraZeneca

BACKGROUND: This supplemental application proposes new information to be added to the Crestor package insert, based on the results of the study entitled, "A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase IIIb Study of Rosuvastatin (Crestor) 20 mg in the Primary Prevention of Cardiovascular Events Among Subjects with Low Levels of LDL- Cholesterol and Elevated Levels of C-Reactive Protein (JUPITER)".

ATTENDEES: Eric Colman, Amy Egan, Mary Roberts, Todd Sahlroot, David Hoberman, Janice Brown (tcon), Wei Qiu, Jaya Vaidyanathan, Paul Tran (tcon), Ginneh Stowe and Margaret Simoneau.

ASSIGNED REVIEWERS (including those not present at filing meeting): none

Discipline/Organization	Reviewer
Medical:	Roberts, MD
Secondary Medical:	Egan, MD
Statistical:	David Hoberman
Pharmacology:	K.Davis-Bruno (NN)
Statistical Pharmacology:	NN
Chemistry:	Janice Brown
Environmental Assessment (if needed):	NN
Biopharmaceutical:	Jaya Vaidyanathan (NN)
Microbiology, sterility:	NN
Microbiology, clinical (for antimicrobial products only):	
DSI:	Yes
OPS:	NN
Regulatory Project Management:	M.Simoneau
Other Consults:	None at filing time

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐

If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known Dec 15, 2009 NO ☐

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS NA FILE ☐ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? ☐ NO ☐

PHARMACOLOGY/TOX N/A ☒ FILE ☐ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☐

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Sterile product? YES ☐ NO ☐
  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments: T-con with AZ and David Hoberman on June 1, 2009 (request for additional information)

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

Margaret Simoneau
Regulatory Project Manager

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Margaret Simoneau
6/17/2009 11:39:33 AM
CSO