CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208647Orig1s000

SUMMARY REVIEW
### Cross-Discipline Team Leader Review

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<td>John Sharretts, M.D.</td>
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<td>Subject</td>
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<td>NDA/BLA # and Supplement#</td>
<td>NDA 208647 – Class 2 Resubmission</td>
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<tr>
<td>Applicant</td>
<td>Sun Pharma Global FZE</td>
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<td>PDUFA Goal Date</td>
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<td>Proprietary Name</td>
<td>Ezallor</td>
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<tr>
<td>Established or Proper Name</td>
<td>Rosuvastatin</td>
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<td>Dosage Form(s)</td>
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**Applicant Proposed Indication(s)/Population(s)**

1. Adjunctive therapy to diet for the treatment of adult patients with hypertriglyceridemia
2. An adjunct to diet for the treatment of adult patients with primary dysbetalipoproteinemia (Type III hyperlipoproteinemia)
3. Adjunctive therapy to other lipid-lowering treatments (e.g., LDL apheresis) or alone if such treatments are unavailable to reduce LDL-C, Total-C, and ApoB in adult patients with homozygous familial hypercholesterolemia

**Applicant Proposed Dosing Regimen(s)**

5, 10, 20, 40 mg

**Recommendation on Regulatory Action**

Approval

**Recommended Indication(s)/Population(s) (if applicable)**

*Not applicable*

**Recommended Dosing Regimen(s) (if applicable)**

*Not applicable*
1. Benefit-Risk Assessment

This is a resubmission of a New Drug Application (NDA) for Ezallor (rosuvastatin) capsules. It is a 505(b)(2) application relying on FDA’s previous findings of safety and efficacy for NDA 021366, Crestor (rosuvastatin calcium) tablets. The proposed indications for Ezallor are identical to those currently approved for Crestor, except for those protected by patent or exclusivity.

In the original NDA submitted August 28, 2015, the applicant submitted data to establish a scientific bridge between its product, rosuvastatin capsules, and the listed drug, Crestor. The clinical package consisted of clinical pharmacology data evaluating bioequivalence between the 40 mg dose of rosuvastatin capsules and Crestor 40 mg. The applicant also submitted biopharmaceutical studies in support of the application, including dissolution data to support a biowaiver for the lower doses (5 mg, 10 mg, and 20 mg), an in-use study of the rosuvastatin sprinkled over applesauce, and an in vitro NG tube study supporting alternate administration of the product. The application also included bridging toxicology data comparing the toxicity profile to that of Crestor. There were no clinical or nonclinical deficiencies noted in the reviews of these studies.

Although the applicant submitted adequate data regarding drug substance, drug product, manufacturing process, and biopharmaceutics, the Office of Pharmaceutical Quality recommended a complete response due to deficiencies identified at one of the proposed manufacturing sites. The Division issued a complete response letter on June 22, 2016.

In this resubmission, the applicant did not conduct any new clinical or nonclinical studies. The applicant submitted a safety update consisting of a review of the published literature and searches of postmarketing databases. The update identified no new safety concerns that would change the benefit-risk assessment of rosuvastatin capsules. Following inspections conducted on June 23, 2018 and October 9, 2018, the OPQ facilities reviewer concluded that the updated manufacturing process and quality testing were acceptable and recommended approval.

Because there are no remaining deficiencies regarding product quality and the applicant has adequately bridged its formulation of Ezallor (rosuvastatin) capsules with the listed drug, I recommend approval of the application for the proposed indications.
2. Background

This is a 505(b)(2) application for a new dosage form of rosuvastatin oral capsule, relying on the Agency’s previous findings of safety and efficacy for NDA 021366, Crestor (rosuvastatin calcium) tablets, originally approved in 2003. The applicant maintains that its product, a hard-gelatin capsule filled with granules of rosuvastatin calcium, will facilitate dosing in patients who find it difficult to swallow a tablet. The product may be swallowed intact, the capsule may be opened and the contents sprinkled onto applesauce, or the contents may be administered in water via a nasogastric tube. The proposed indications are identical to those of Crestor, except for those indications protected by patent or exclusivity.

The applicant originally submitted the NDA on August 28, 2015. The review team for the original submission concluded that the applicant demonstrated bioequivalence between its product, rosuvastatin capsules, and the listed drug, Crestor (rosuvastatin) tablets. Although there were no clinical deficiencies, the Office of Product Quality recommended a complete response due to deficiencies regarding a manufacturing facility for the drug product. The Division issued a complete response on June 22, 2016. Refer to the Division Director’s Summary Review dated June 22, 2018, and the individual discipline primary reviews for details.

The applicant requested and received an extension of the date to resubmit the application to address the deficiencies in the complete response until June 30, 2018. The applicant submitted this application on June 18, 2018. There was no other significant regulatory history since the complete response.

3. Product Quality

The Office of Pharmaceutical Quality (OPQ) recommended approval of the application in the Integrated Quality Assessment. Refer to the complete document and summary compiled by the technical lead, Christopher Galliford, Ph.D., and dated December 18, 2018, for details.

The original submission of this application on August 28, 2015 resulted in a complete response due to cGMP deficiencies identified at the proposed drug project manufacturer, Sun Pharmaceutical Industries Limited, Halol-Baroda 389350, Gujarat, India.

Inspections conducted as part of this resubmission included a GMP inspection completed on March 9, 2018 classified VAI, and a Pre-Approval Inspection completed June 23, 2018 classified VAI. The facilities reviewer concluded that the manufacturing process and quality testing were acceptable and recommended approval based on the updated information on October 9, 2018. Dr. Galliford reported minimal changes to the drug substance, drug product, dosage form, or route of administration in the resubmitted application, and referenced the review of the original submission dated May 18, 2016 in his summary.

In the OPQ Integrated Quality Assessment of the original submission dated May 18, 2016, the review team concluded that there were no deficiencies with regards to the drug substance, drug...
product, manufacturing process, and biopharmaceutics. The biopharmaceutics reviewer, Vincent (Peng) Duan, Ph.D., concluded that the bio waiver requests for the lower strengths (5 mg, 10 mg, and 20 mg) were acceptable pending acceptance of the bioequivalence studies conducted with the 40 mg strengths. Refer to the Clinical Pharmacology section of this review regarding the bioequivalence studies. The biopharmaceutics reviewer also found the results of an in-use study of rosuvastatin sprinkled on applesauce and an in vitro NG tube dissolution study using a NG tube acceptable.

The chemical name for rosuvastatin calcium is (3R, 5S)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl]-3,5-dihydroxy-6(E)-heptenoic acid calcium salt (2:1). The molecular formula is C44H54F2N6O12S2•Ca, and the molecular weight is 1001.14 (salt)/963.08 (base). The drug product is a hard gelatin capsule filled with rosuvastatin calcium granules. The different strengths differ by the amount of granules per capsule and the capsule shell size. For additional details, refer to the OPQ Integrated Assessment dated December 18, 2018.

4. Nonclinical Pharmacology/Toxicology

The applicant did not submit any new nonclinical data in support of this application. In the original submission, the applicant submitted a 14-day dose range finding (non-GLP) rat toxicology and pivotal GLP-compliant 30-day bridging rat toxicology study. The Nonclinical reviewer for the original submission, Stephanie Leuenroth Quinn, Ph.D., concluded that the pivotal study demonstrated similar toxicity profiles between the test article (rosuvastatin) and the listed drug, Crestor. Refer to her review dated August 28, 2015 for details.

5. Clinical Pharmacology

The applicant did not conduct any new clinical pharmacology studies in support of this application. In the original submission, the applicant submitted two pivotal bioequivalence (BE) studies, one under fasting conditions and one under fed conditions, to assess the BE between rosuvastatin 40 mg capsules (both intact and sprinkling the contents over applesauce) versus Crestor 40 mg tablets. The applicant requested a bio waiver relying on in vitro dissolution data submitted for the lower strengths (5 mg, 10 mg, and 20 mg). The Clinical Pharmacology reviewer for the original application, Shalini Wickramaratne Senarath Yapa, Ph.D., concluded that applicant demonstrated bioequivalence between rosuvastatin 40 mg capsules and Crestor 40 mg tablets, and recommended approval. Refer to her review dated May 23, 2016 for details. The biopharmaceutics reviewer concluded that the dissolution data supported approval of the lower strengths and accepted the findings of dissolution data evaluating use of drug granules as sprinkles on applesauce and as an aqueous suspension for NG tube administration. Refer to the Product Quality section of this review for a summary and to the OPQ Integrated Quality Assessment dated May 18, 2016 for details.

For the current submission, Dr. Wickramaratne Senarath Yapa reviewed the proposed labeling and provided comments regarding Sections 2 (Dosing and Administration), 7 (Drug Interactions), and 12 (Clinical Pharmacology). Refer to her review dated December 13, 2018, for details.
6. **Clinical Microbiology**

This section is not applicable. Refer to the assessment of microbiology within the OPQ integrated assessment of the original submission, dated May 18, 2016 for details. The review found the microbiology information acceptable.

7. **Clinical/Statistical- Efficacy**

This section is not applicable. The applicant did not submit any new efficacy data with this submission.

8. **Safety**

The applicant did not conduct any new clinical studies for this submission. In the original submission, the applicant submitted safety data from the pivotal clinical pharmacology studies. The clinical reviewer, Mary Roberts, M.D., concluded that the safety profile of rosuvastatin capsules was consistent with the known safety profile of the listed drug, Crestor (rosuvastatin) tablets. Refer to her review dated May 26, 2017 for details.

With the current submission, the applicant provided an updated safety assessment, consisting of a review of published literature and pharmacovigilance databases. Dr. Roberts reviewed the submission, and concluded that there were no new safety concerns which would change the benefit-risk profile of rosuvastatin capsules. She recommends for approval. Refer to her review of the current submission, dated December 17, 2018 for details.

9. **Advisory Committee Meeting**

This section is not applicable. An Advisory Committee meeting was not necessary for this 505(b)(2) resubmission.

10. **Pediatrics**

Because this NDA is for a new dosage form, the Pediatric Research Equity Act (PREA) requires a pediatric assessment for the proposed indications, unless waived, deferred, or inapplicable. The applicant previously had an agreed initial pediatric study plan (iPSP) with the Agency with a plan to request a full waiver of PREA required studies for the proposed indications because pediatric trials would be impossible or highly impractical.

Subsequent to the agreed iPSP, however, the innovator conducted a study of pediatric patients ages 7 to 17 years with homozygous familial hypercholesterolemia (HoFH). On May 27, 2016, the Division approved an efficacy supplement (NDA 021366/S-033) adding a new indication to the Crestor label for treatment of pediatric patients ages 7 to 17 years of age with HoFH. The innovator has exclusivity for the pediatric HoFH indication until May 27, 2023.
In light of the new pediatric data, the Division of Pediatric and Maternal Health (DPMH) recommended revising the justification for not conducting pediatric trials under PREA. DPMH recommend granting a full waiver of studies of HoFH in patients less than 7 years of age, and a deferral for patients 7 years and older until the pediatric and orphan exclusivities expire. The Pediatric Review Committee (PeRC) PREA subcommittee reviewed the application on December 12, 2018 and granted the waiver in patients less than 7 years and deferral in patients ages 7 to 17 years.

As noted above, Crestor has orphan drug exclusivity for HoFH in pediatric patients until May 27, 2023. Although information about use of rosuvastatin in pediatric patients with HoFH is protected, DPMH concluded that this application could be approved without the protected pediatric use information related to pediatric HoFH and HeFH. DPMH recommended including disclaimer language wherever pediatric information regarding HoFH is “carved out” of the label. Refer to the DPMH review dated December 13, 2018 for details.

11. Other Relevant Regulatory Issues

In addition to the indications the applicant is seeking, the listed drug Crestor is approved for the following indications protected by patent or exclusivity:

- Adjunctive therapy to diet to reduce elevated Total-C, LDL-C, ApoB, nonHDL-C, and triglycerides and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia
- To reduce Total-C, LDL-C and ApoB levels in children and adolescents 8 to 17 years of age with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present: LDL-C >190 mg/dL, or >160 mg/dL along with a positive family history of premature cardiovascular disease (CVD) or two or more other CVD risk factors
- To reduce LDL-C, Total-C, nonHDL-C and ApoB in children and adolescents 7 to 17 years of age with homozygous familial hypercholesterolemia, either alone or with other lipid-lowering treatments (e.g., LDL apheresis)
- As adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower total-C and LDL-C
- To reduce the risk of stroke, myocardial infarction, and arterial revascularization procedures in patients without clinically evident CHD, but with increased risk of cardiovascular disease based on age, hsCRP, and at least one additional cardiovascular risk factor such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease (primary prevention)

In the original resubmission, the applicant [4(b)] On October 26, 2018, following an information request from the Division for updated patient certification, the applicant [4(b)]
12. Labeling

Proprietary Name

The applicant requested a review of the proposed proprietary name, Ezallor. The Division of Medication Error Prevention and Analysis (DMEPA), found the name acceptable. Refer to the DMEPA review dated September 13, 2018.

Prescribing Information

The applicant submitted draft labeling similar to that of the listed drug Crestor. Major differences between the proposed Ezallor label and the Crestor label included exclusion of indications for Crestor protected by patent or exclusivity, administration information regarding use of the capsule contents as sprinkles either for oral administration or via NG tube, removal of protected pediatric information, and addition of disclaimers in those locations where pediatric information was carved out.

During labeling negotiations, the Clinical Pharmacology review team recommended revisions to the Dosage and Administration Section (2.3), regarding instructions for use of the capsule as sprinkles, as well as changes to Drug Interactions (Section 7), and Clinical Pharmacology (Section 12) to align with the most recently updated Crestor level. Refer to the Clinical Pharmacology Review for details.

DMEPA made recommendations throughout the label regarding throughout the label to minimize the risk of medication errors. Refer to the DMEPA review dated November 9, 2018 for details.

DPMH made recommendations regarding pediatric information carved out from the label and appropriate use of disclaimers. Major changes instituted from the DPMH recommendations included removal of pediatric adverse event information from Pediatric Use (Section 8.4). DPMH also recommended removal of juvenile toxicology study information from Animal Toxicology and/or Pharmacology (Section 12.3), but ultimately the Division maintained the animal information along with a disclaimer in place of pediatric human dose information carved out of the section. The Office of the Chief Counsel (OCC) recommended keeping the toxicology information to maintain consistency between this NDA product and approved rosuvastatin ANDA products also relying on Crestor as the reference listed drug. Refer to the DPMH review for details.

Other Labeling

The Patient Labeling Review completed by the Division of Medical Policy Programs (DMPP) and Office of Prescription Drug Promotion (OPDP) reviewed the proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for wording, clarity, consistency with the Prescribing Information, elimination of redundancy, and elimination of promotional language.
The major changes recommended in the Patient Labeling review were to relocate the IFU into a separate document and to reword the IFU with more patient-friendly language. OPDP also recommended removal of potentially promotional disclaimer language regarding pediatric marketing exclusivity for Crestor, but the Division retained the disclaimer to maintain consistency with approved generic rosvastatin products on the advice of OCC. Refer to the Patient Labeling Review dated December 14, 2018 for details.

13. **Postmarketing Recommendations**

*Risk Evaluation and Management Strategies (REMS)*

This section is not applicable. The product does not require a REMS to ensure that the benefits outweigh the risks or to ensure safe use.

*Postmarketing Requirements (PMRs) and Commitments (PMCs)*

Because of PREA requirements, the application requires the following PMR for approval:

1) Assessment of Ezallor (rosuvastatin capsules) for the treatment of homozygous familial hypercholesterolemia in pediatric patients ages 7 to 17 years of age (inclusive).

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Because the originator, Crestor, conducted a clinical study in the pediatric HoFH population, the applicant may not obtain a waiver using the rationale that pediatric trials in the population would be impossible or highly impractical. The applicant may not reference the pediatric study, which is protected by exclusivity. Furthermore, patent or exclusivity protection of previously conducted clinical studies is not among the criteria for a waiver specified in PREA. Instead, the Agency issued a deferral for the requirement to address PREA for the pediatric HoFH indication until the expiration of the orphan exclusivity in May 2023.

14. **Recommended Comments to the Applicant**

None
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN M SHARRETTS  
12/18/2018

WILLIAM H CHONG  
12/18/2018

Agree with Dr. Sharretts. This CDTL serves as the Divisional memo. The recommended population and dosing is the same as the applicant's proposed population and dosing.