CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213072Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	3/14/2021
From	Jayabharathi Vaidyanathan, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 213072
Applicant	Althera Pharmaceuticals Industries Limited
Date of Submission	9/23/2020
PDUFA Goal Date	3/23/2021
Proprietary Name / Established (USAN) names	Roszet/rosuvastatin and ezetimibe tablets
Dosage forms / Strength	Fixed dose immediate release tablets, 40/10 mg, 20/10mg, 10/10 mg and 5/10 mg rosuvastatin/ezetimibe
Proposed Indication(s)	Treatment of primary non-familial hyperlipidemia and homozygous familial hypercholesterolemia
Recommended Action:	Approval

1. Introduction

On July 29, 2019, the applicant (Althera Pharmaceuticals Industries Limited) submitted NDA 213072 via the 505(b)(2) pathway for Roszet (rosuvastatin and ezetimibe) fixed-dose combination (FDC) tablets indicated for the treatment of primary non-familial hyperlipidemia and homozygous familial hypercholesterolemia (HoFH). Rosuvastatin is a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor and ezetimibe is an inhibitor of intestinal cholesterol absorption. To support their 505(b)(2) NDA application, the applicant is relying on FDA's previous finding of safety and effectiveness for approved listed drugs, Crestor (rosuvastatin) and Zetia (ezetimibe) and have conducted three clinical relative bioavailability studies using rosuvastatin/ezetimibe FDC tablets compared to the co-administration of the individual reference products. Biowaiver is being requested for the strengths that were not evaluated in the clinical studies. The proposed tablet strengths include 40/10 mg, 20/10mg, 10/10 mg and 5/10 mg rosuvastatin/ezetimibe tablets.

A Complete Response (CR) letter was sent for this NDA on May 27, 2020 due to facility related deficiencies identified during inspection of (b) (4) and (b) (4). An End of Review Type A meeting was held on June 29, 2020 and the applicant received guidance from the Agency on their plan to resolve the CR letter issues.

The applicant resubmitted the application on September 23, 2020 with response to the deficiencies.

2. Background

Refer to CDTL review of the original NDA for regulatory background leading up to the original NDA submission (see Dr. Vaidyanathan's review- REV-SUMMARY-10 (Division Director Review); REV-SUMMARY-09 (CDTL Review) DATED 5/14/2020 in DARRTS).

The NDA was discussed at the CDER 505(b)(2) committee and there were certain issues identified with respect to the indications proposed by the applicant and the patent certifications. An information request was sent to the applicant on 2/22/2021 to align the patent certifications with the proposed labeling. In addition, the applicant was requested to amend the patent certifications with respect to the '618 patent listed for Crestor NDA 21445 and the '058 patent listed for Zetia NDA 21445. A teleconference was held, with the applicant to discuss the patent certifications on March 1, 2021. The sponsor resubmitted the labeling on 3/10/2021.

3. Quality (CMC/Device)

The recommendation from the Office of Pharmaceutical Quality (OPQ) for NDA 213072 is approval, which includes acceptable recommendation for the facilities listed in the application (see Dr. Ramaswamy's Integrated Quality Assessment dated 2/18/2021 in DARRTS).

The CR letter required satisfactory resolution of the facility deficiencies, revalidation of chromatographic methods, and acceptable stability data before this application could be approved. In addition, the CR letter contained comments related to the manufacturing batch record. There were no deficiencies associated with the drug substance and biopharmaceutics sections of this NDA in the first review cycle. Refer to the OPQ integrated quality review dated 4/20/2020 in DARRTS for details.

The applicant revalidated the chromatographic methods used for releasing the product and transferred them to the drug product manufacturer. The proposed methods were found to be acceptable for quality control purpose. The stability of the product was reviewed, and 24 months shelf-life was granted for the drug product packaged in 30ct HDPE bottles, when stored at 20° to 25°C. It was also concluded that the dissolution data showed that the drug product manufactured from the two sources (new facility ((b) (4)) and withdrawn facility ((b) (4))) of drug substance are comparable. Review of the batch formula, manufacturing process/in-process control information, updated batch record information as well as facility information provided in the original submission and in the resubmission was conducted. Overall the process and facilities information provided in the NDA was acceptable.

There are no outstanding deficiencies related to drug substance, drug product, process, biopharmaceutics, and facilities, the OPQ overall recommendation for NDA 213072 is approval (see Dr. Ramaswamy's Integrated Quality Assessment dated 2/18/2021 in DARRTS).

4. Nonclinical Pharmacology/Toxicology

As per Pharmacology/Toxicology reviewers, the nonclinical studies submitted with this NDA and previous FDA findings of the safety and efficacy for Crestor and Zetia are adequate to support approval of Roszet. The nonclinical review concluded that there are no nonclinical concerns for the FDC tablets (see REV-NONCLINICAL-21 (Primary Review) dated 5/4/2020 in DARRTS). No new nonclinical data has been submitted in the resubmission.

5. Clinical Pharmacology/Biopharmaceutics

The applicant's original NDA submission included the results of three relative bioavailability studies. These studies establish a scientific bridge for the proposed FDC tablets to reference the efficacy and safety findings of the individual reference products (US approved Crestor and US approved Zetia). Overall, the clinical pharmacology review concluded that the results of the studies established bioequivalence between the proposed FDC tablets and the individual reference products, Crestor and Zetia. Refer to clinical pharmacology review (see REV-CLINPHARM-21 (Primary Review) dated 4/20/2020 in DARRTS). No new clinical pharmacology data has been submitted in the resubmission.

6. Clinical Efficacy & Safety

There are no new clinical efficacy or safety data essential for the risk/benefit assessment of rosuvastatin/ezetimibe fixed dose combination tablets. The proposed dose and dosing regimen for Roszet combination product is consistent with doses approved for rosuvastatin and ezetimibe. Overall, the observed events were consistent with the known safety profiles of rosuvastatin and ezetimibe. The clinical reviewer concludes that Roszet is approvable based on a favorable benefit/risk framework (See REV-CLINICAL-21 (Primary Review) dated 5/5/2020 in DARRTS).

7. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application.

8. Pediatrics

The applicant submitted NDA 213072 without an Agreed iPSP or a pediatric assessment. The Division consulted the Division of Pediatric and Maternal Health (DPMH) to opine on a path forward regarding the development of a pediatric assessment plan for the FDC product. This proposed product contains a novel combination which is considered to be a new active ingredient under the Pediatric Research Equity Act (PREA). Therefore, the applicant is required to submit a pediatric assessment with the adult NDA or an Agreed initial Pediatric Study Plan (iPSP) describing how it plans to evaluate dosing, safety, and efficacy of this

product in the pediatric population, including any plans to request partial waivers and/or deferral of PREA study requirements for a specific pediatric age group.

FDA approved Crestor for the following use in pediatric patients:

- Treatment of HeFH in patients 10 to 17 years of age in 2009 with expansion of the indication down to 8 years of age and older in 2014
- Treatment of HoFH in patients 7 years of age and older. FDA granted Crestor pediatric exclusivity for the HeFH indication that will expire June 2022
- FDA also granted Crestor pediatric orphan exclusivity for HoFH. This orphan exclusivity expires May 2023

FDA approved Zetia (ezetimibe 10 mg) in 2008 to allow

- Co- administration with approved pediatric doses of a statin in pediatric patients 10 to 17 years of age with HeFH

To date, ezetimibe has not been approved either as monotherapy or for co-administration with statins for the treatment of pediatric patients with HoFH. Therefore, there is no approved pediatric use information for Zetia for the treatment of HoFH.

The application was discussed at the Pediatric Review Committee (PeRC) meeting on 03/16/2021. The PeRC agreed with a waiver for pediatric patients with non-familial hyperlipidemia because studies are impossible or highly impractical; extreme cholesterol elevations requiring pharmacologic intervention are uncommon in children outside of inherited familial disorders, and lifestyle intervention remains first-line therapy in pediatric non-familial. The PeRC concluded that the applicant must submit an assessment for pediatric patients, aged 2 to 17, with HoFH, but the assessment may be deferred until expiration of pediatric orphan exclusivity for Crestor. The pediatric assessment will be issued as a PMR, and DDLO and the PeRC must agree to the components of the assessment prior to approval.

9. Other Relevant Regulatory Issues

OSIS inspection

The Office of Study Integrity and Surveillance (OSIS) inspected the analytical portions of studies (b) (4)-083-18, (b) (4)-084-18, and (b) (4)-085-18 during (b) (4) and no objectional conditions or practices were founds during the inspection and the final inspection classification was No Action Indicated (NAI). OSIS concluded that the data from the audited studies are reliable to support a regulatory decision (see REV-DSI-05 (Bioequivalence Establishment Inspection Report Review) in DARRTS dated 04/17/2020).

Financial Disclosure

FDA 3454 form was submitted confirming that the applicant of the submitted studies did not enter into any financial arrangement with the listed clinical investigators that could influence the outcome of the trial.

Proprietary name

Division of Medication Error Prevention and Analysis (DMEPA) has reassessed the proprietary name, Roszet which was found conditionally acceptable previously (see REV-SURVEPI-10 (Proprietary Name Review) in DARRTS dated 11/01/2019). Based on the reassessment, DMEPA has concluded that the name is acceptable (see REV-SURVEPI-10 (Proprietary Name Review) in DARRTS dated 12/3/2020).

10. Labeling

DMEPA reviewed the resubmitted labels for Roszet to determine if they are acceptable from a medication error perspective and determined the package insert, container labels and (b) (4) were acceptable (REV-SURVEPI-06 (Labeling Review) dated 1/14/2021, 1/28/2021, and 2/9/2021 in DARRTS).

The major labeling comments included:

- Revision of the indication and usage section to correspond to the patent certifications.
- (b) (4) . (b) (4) .
- Updating the label to current labeling standards

11. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

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/

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03/17/2021 03:42:20 PM

JOHN M SHARRETTS
03/17/2021 04:57:54 PM
This review serves as the decisional memo for the application.