Division of Diabetes, Lipid Disorders, and Obesity

NDA	208647/S-006; -007, -008, -009, -010, 011
Drug	Ezallor Sprinkle (rosuvastatin capsules)
Sponsor	Sun Pharmaceutical Industries Limited
Supporting Documents	SD# 99, 108, 111, 114, 116-120
Topic	Labeling supplements S-006: removal of pregnancy contraindication S-007: Addition of pediatric HoFH indication S-008: Addition of CV risk reduction S-009: Addition of primary hyperlipidemia indication S-010: Addition of slow progression of atherosclerosis indication S-011: Addition of pediatric HeFH indication
Date	28 September 2021; 3 August 2022; 3 January 2022; 13 April 2023
Clinical Reviewer	Mary Roberts, MD
Team Leader	Eileen Craig, MD

Sun Pharmaceutical Industries Limited has submitted labeling supplements for Ezallor Sprinkle which seek indications that are no longer under patent and/or exclusivity protection and revise the label to be consistent with Crestor, the reference listed drug (RLD).

Background

In the initial application cycle, the Ezallor sponsor established bioequivalence between Ezallor and Crestor. There were no clinical, clinical pharmacology, or non-clinical deficiencies (please see the clinical review dated May 27, 2016, for further details). However, the Office of Pharmaceutical Quality (OPQ) recommended a complete response due to deficiencies at the manufacturing facility. A Complete Response Letter was issued June 22, 2016. In a Class 2 resubmission addressing CMC deficiencies, Ezallor was approved via a 505b2 pathway with the following indications in 2018.

- Hypertriglyceridemia: Adjunctive therapy to diet for the treatment of adult patients with hypertriglyceridemia
- Primary dysbetalipoproteinemia (Type III hyperlipoproteinemia): An adjunct to diet for the treatment of patients with primary dysbetalipoproteinemia
- Homozygous familial hypercholesterolemia (HoFH): 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

During the first review cycle, the Ezallor application was taken to the Pediatric Review Committee (PeRC) on 18 November 2015 and was granted a full waiver for pediatric studies for the sought after treatment indications (which included HoFH) because studies are impossible or highly impractical. However, in 2017, the innovator conducted a trial using Crestor to treat pediatric patients 7 years to 17 years of age with HoFH and received a pediatric HoFH treatment indication. Therefore, it was the opinion of DDLO during the second review cycle of Ezallor that the justification for not conducting pediatric trials under PREA for this indication should be revised. The PeRC reviewed the Ezallor application during the second review cycle on 12 December 2018. A partial waiver of studies of HoFH in patients from birth to less than 7 years of age because studies would be impossible or highly impractical was granted, as well as a deferral for patients 7 years and older until the pediatric and orphan exclusivities expire. Once this exclusivity expires on May 27, 2023, the labeling was to be updated to include the protected pediatric information and the PREA requirement could be considered fulfilled. PMR 3559-1 was issued with the approval of Ezallor as follows:

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

The sponsor has submitted labeling with the following indication and supporting information related to the Orange Book (OB) exclusivity and to comply with the PMR.

- As an adjunct to other LDL-C-lowering therapies, or alone if such treatments are unavailable, to reduce LDL-C in adults and pediatric patients aged 7 years and older with homozygous familial hypercholesterolemia (HoFH).

In addition, the sponsor has submitted the following information related to the expired OB patent (6858618*PED; Expiration date: June 17, 2022) which are included in labeling supplements -008, -009, -010, and -011

- To reduce the risk of stroke, myocardial infarction, and arterial revascularization procedures in adults without established coronary heart disease who are at increased risk of cardiovascular (CV) disease based on age, hsCRP ≥2 mg/L, and at least one additional CV risk factor.
- As an adjunct to diet to reduce LDL-C in adults with primary hyperlipidemia.
- As an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C) and slow the progression of atherosclerosis in adults.
- As an adjunct to diet to reduce LDL-C in adults and pediatric patients aged 8 years and older with heterozygous familial hypercholesterolemia (HeFH).

The Agreed iPSP for this product requested a full waiver for CV risk reduction, primary hyperlipidemia, and slowing the progression of atherosclerosis, (b) (4) because studies are impossible or highly impracticable. Please note in November 2015, the pediatric HeFH indication for the innovator product was extended down to 8 years of age. There was not a deferral request submitted with the labeling supplement for pediatric HeFH patients 10 (or 8) years old or greater until pediatric exclusivities expired.

This application was brought before the PeRC on June 27, 2023. The PeRC agreed that PMR 3559-1 was fulfilled for the pediatric HoFH indication with the submission of the updated label and no PMR was needed for the pediatric HeFH indication. Labeling for the pediatric HeFH indication could be granted to the Ezallor label if the Division agreed following regulatory review.

Please note the Ezallor label was also updated to include recent changes to the innovator label in the postmarket section 6.2 regarding myasthenia gravis. The 505b2 committee has reviewed the sponsor's application and concluded that it is cleared for action. Final labeling is pending.

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/s/

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