CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206679Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	*See electronic stamp*
From	James P. Smith, MD, MS
Subject	Summary Review for Regulatory Action
NDA#	206679
Applicant	Rosemont Pharmaceuticals Ltd., a Perrigo Company
Date of Submission	22 June 2015
PDUFA Goal Date	22 April 2016
Proprietary Name / Established (USAN) names	Simvastatin Oral Suspension / simvastatin
Dosage forms / Strength	Suspension; 20 mg/5 mL and 40 mg/5 mL
Proposed Indications	Reduction in Risk of CHD Mortality and Cardiovascular Events; Hyperlipidemia (multiple indications); Adolescent Patients with Heterozygous Familial Hypercholesterolemia See labeling for details.
Recommended:	Approval

Material Reviewed/Consulted & Primary Reviewer(s)		
Clinical Pharmacology Review	17 Mar 2016	S.W. Johnny Lau, RPh, PhD
OPQ Review	17 Mar 2016	Suong Tran, PhD (Team Lead); See review for listing of quality review team
Medical Officer Review	08 Apr 2016	Eileen Craig, MD
Pharmacology/Toxicology Review	22 Mar 2016	C. Lee Elmore, PhD
OSIS Memo	27 Aug 2015	Shila S. Nkah
OSE/DMEPA Label & Labeling Reviews	14 Sep 2015 17 Feb 2016 08 Apr 2016	Nicole B. Garrison, PharmD, BCPS

OPQ: Office of Pharmaceutical Quality; OSIS: Office of Study Integrity and Surveillance; OSE: Office of Surveillance and Epidemiology; DMEPA: Division of Medication Error Prevention and Analysis

Introduction / Background

The applicant is seeking approval of Simvastatin Oral Suspension via the 505(b)(2) regulatory pathway, relying on the Agency's previous determination of safety and effectiveness for Zocor (simvastatin) tablets, which was approved on 23 December 1991 (NDA 19766). The proposed indications are identical to the listed drug. The applicant has developed two strengths of suspension: 20 mg/5 mL and 40 mg/5 mL. All review disciplines have recommended approval.

CMC

The recommendation from the Office of Pharmaceutical Quality (including the manufacturing inspection recommendation) is for approval. According to the OPQ review, there are no unresolved deficiencies. I concur that there are no outstanding issues that would preclude approval.

The only novel excipient in the drug product is strawberry flavoring, with CMC information in a DMF that was found acceptable. See the OPQ review for a description of other excipients in this formulation. The regulatory drug product specification was found adequate based on the supporting release and

stability data and ICH guidelines for this type of dosage form. To reflect the conditions used in the analytical methods for Particle Size Distribution and Resuspendability, labeling will include the instruction "Shake well for at least 20 seconds."

Stability testing supports an expiry of 24 months at room temperature; after initial use, up to one month at room temperature. Labeling will include the instruction "Protect from heat" based on stability data.

A biowaiver request was submitted for the 20 mg/5 mL strength. According to the OPQ review, the two strengths are not dose-proportional but have the same inactive ingredients with minor differences in the amounts. The two strengths have similar in vitro dissolution profiles. Thus, according to the biopharmaceutics reviewer, given that the clinical pharmacology review concluded bioequivalence between the higher strength (40 mg/5 mL) and Zocor 80 mg (see below), the biowaiver request for the lower-strength drug product should be granted.

Pharmacology/Toxicology

Dr. C. Lee Elmore reviewed this application from the pharmacology/toxicology perspective and recommends approval. No nonclinical studies were submitted to support a scientific bridge between Simvastatin Oral Suspension and Zocor to establish safety; instead, the applicant is relying upon physicochemical characterization or has provided scientific justification for the safety of all components of Simvastatin Oral Suspension. No impurities or degradants were identified in the drug substance or drug product for Simvastatin Oral Suspension that required qualification. No leachables or extractables of toxicological concern were identified. In his review, Dr. Elmore discusses two excipients (ethylparaben and propylparaben) at levels preliminary identified as potentially exceeding levels listed in the FDA Inactive Ingredient Database (IID) and a novel flavoring that was not found in the IID. Dr. Elmore concluded that the levels of these excipients are safe for chronic administration; see his review for details. I concur that there are no outstanding pharm/tox issues that would preclude approval.

Clinical Pharmacology

Dr. S.W. Johnny Lau reviewed this applicant from the clinical pharmacology perspective and recommends approval, with labeling to specify that the product should be taken once a day in the evening on an empty stomach because of a significant effect of food on the exposure of simvastatin suspension.

The sponsor conducted 2 studies that support this application:[1]

- PRG-NY-14-010: Bioequivalence between 80 mg Simvastatin Oral Suspension (10 mL of 40 mg/5 mL) and 80 mg simvastatin tablet (Zocor) under fasting conditions; and
- PRG-NY-14-010: Relative bioavailability of 80 mg Simvastatin Oral Suspension (10 mL of 40 mg/5 mL) under fasting vs. high-fat meal conditions; and

PRG-NY-14-010 was a 2-treatment, 3-period, 3-way crossover study in healthy men. Each participant received 80 mg Zocor (reference) during two periods and 80 mg Simvastatin Oral Suspension (test) during one period. The applicant pre-specified that they would use the reference-scaled bioequivalence approach to assess BE between their product and the listed drug. Although this was an atypical

[1] A third study that compared the relative bioavailability between 20 mg/5 mL Simvastatin Oral Suspension with the 20 mg Zocor tablet *marketed in the UK* was not reviewed, since the comparator was not the U.S. listed drug.

approach for a simvastatin-containing product, Dr. Lau determined that it was acceptable and concluded that the data from this study support bioequivalence between the test and reference products with respect to simvastatin C_{max}, AUC_{0-t}, and AUC_{0-inf}. With respect to the metabolite simvastatin acid, the reference-scaled bioequivalence approach did not demonstrate equivalence for Cmax between test and reference, but it did for the AUCs. Because bioequivalence with respect to the metabolite are used as supportive data, Dr. Lau found these data acceptable and concluded that 80 mg Simvastatin Oral Suspension (40 mg/5 mL) is bioequivalent to 80 mg Zocor.

PRG-NY-14-011 was a 2-treatment, 2-period, 2-sequence crossover study in healthy men and women, which assessed the effect of food (high-fat meal) on the bioavailability of 80 mg Simvastatin Oral Suspension (40 mg/5 mL). This study demonstrated a significant food effect, with lower Cmax and AUCs for simvastatin after a high-fat meal compared with fasting (geometric mean ratios decreased 26.4% and 17.5% for C_{max} and AUC_{0-inf}, respectively); in contrast, C_{max} and AUC_{0-inf} for the metabolite simvastatin acid increased 73.2% and 43.8%, respectively, after a high-fat meal. In light of these data, Dr. Lau recommends that this product be labeled to take in the evening on an empty stomach.

I concur with the reviewers that there are no outstanding issues related to clinical pharmacology that would preclude approval.

Clinical Microbiology

The Division of Microbiology Assessment reviewed this application and found the microbiology information acceptable, recommending approval from a microbiology perspective. I agree that there are no outstanding issues related to microbiology.

Clinical

Dr. Eileen Craig reviewed this application from a clinical perspective and recommends approval. She identified no safety concerns in the BE/BA studies. Because Simvastatin Oral Suspension is approved for marketing in the U.K. and Ireland, the applicant was asked to provide information on adverse events observed in this postmarketing database. These data were provided in the initial Pediatric Study Plan under PIND (b) (4) and the pre-NDA briefing package (February 2014). Dr. Craig noted, "No adverse events were included in this submission that would change the risk-benefit assessment of simvastatin, administered as an oral suspension. No pattern suggestive of previously unknown adverse drug effect of simvastatin was noted."

Dr. Craig's review summarizes labeling suggestions. She concurs with the clinical pharmacology team's recommendation to label this product to take on an empty stomach, given the results of the food-effect study. In addition, she highlights a potential safety concern that it could be much easier for a patient/caregiver to inadvertently administer more than the prescribed dose since they will measure out a volume of suspension instead of taking a tablet that contains the intended dose. She recommends, therefore, that patients be advised to measure Simvastatin Oral Suspension with an accurate measuring device and that a household teaspoon is not an accurate measuring device and could lead to overdosage. I concur with this recommendation.

Pediatrics

This product triggers PREA since it is a new dosage form. A full waiver will be granted for all indications (except HeFH) on the basis that necessary studies would be impossible or highly impractical. For HeFH, a partial waiver will be granted in patients 0-9 years (for the same reason); the product will be labeled for patients with HeFH 10 to 17 years of age, similar to the listed drug.

This plan was reviewed by PeRC on 17 February 2016 and found to be acceptable.

Other Regulatory Issues

The Office of Study Integrity and Surveillance/ Division of New Drug Bioequivalence Evaluation recommended accepting data without on-site inspections because of recent inspections of both the clinical and analytical sites (b) (4) The inspectional outcome for the clinical facility was classified NAI, and although the outcome for the analytical facility was classified VAI, "based on the nature of the findings from our inspection and our recommendation to the review division, an inspection of the analytical site will not be needed at this time."

Regarding financial disclosures, Dr. Craig noted that the applicant provided a signed form FDA 3454 certifying that no financial arrangements or interests were held by the listed clinical investigators for the clinical pharmacology studies conducted to support approval of this application.

Labeling was reviewed by DMEPA and, following revision, ultimately found acceptable from a medication error perspective.

Discussion / Regulatory Recommendation

The applicant has satisfactorily demonstrated that Simvastatin Oral Suspension is bioequivalent to the listed drug, Zocor tablets, and has otherwise met all regulatory requirements for approval with reliance on the Agency's previous determination of safety and effectiveness of Zocor (NDA 19766). There are no outstanding CMC, pharm/tox, clinical pharmacology, or clinical issues.

This application should be approved.

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

/s/

JAMES P SMITH
04/21/2016