CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206679Orig1s000

MEDICAL REVIEW(S)

Medical Officer 505(b)(2) NDA Review
Division of Metabolism and Endocrinology Products

NDA – 206679 (IND (b) (4))

Name of drug – Simvastatin (simvastatin oral suspension, 20 mg/5 mL; 40 mg/5 mL)

Applicant – Rosemont Pharmaceuticals, Ltd / Perrigo Pharmaceuticals

Date of Submission – June 22, 2015

PDUFA Goal Date – April 22, 2016

Medical Reviewer – Eileen M. Craig, M.D.

BACKGROUND

In 2012, Rosemont Pharmaceuticals Ltd. was acquired by Perrigo Pharmaceuticals and became a wholly owned subsidiary. Rosemont Pharmaceuticals Ltd. is the sponsor of this 505(b)(2) NDA application with Perrigo Pharmaceuticals acting on behalf as the US Agent, as well as managing the marketing and distribution of Simvastatin Oral Suspension within the United States and its territories.

The applicant states that Simvastatin Oral Suspension, 20 mg/5 mL and 40 mg/5 mL, was developed as an alternative dosage form for ease of administration to patients who, due to illness or age, may have difficulty swallowing a tablet or prefer a liquid formulation. The sponsor also states that the formulation also provides the physician or pharmacist the option of prescribing a single strength that can accommodate dose titration by volume instead of prescribing tablets of multiple strengths. Simvastatin 20 mg/5 ml and 40 mg/5 ml Oral Suspension is a pharmaceutical alternative formulation of simvastatin that has the same indications and dosing regimens as the listed drug (LD), Zocor® Tablets.

This reviewer sees this simvastatin suspension as a convenience formulation. Under the iPSP review, the sponsor was asked to perform a FAERS database search and compare all available data relating to swallowing difficulties with simvastatin tablets in both the pediatric and adult populations. The Preferred Terms (PTs) used in the database search were choking, gagging/retching, oesophageal injury, foreign body aspiration, and odynophagia (painful swallowing). Adverse events related to swallowing difficulties were similar between the pediatric (0.20%) and adult populations (0.31%). The PubMed, Embase and internet search engines were also used to identify any evidence with respect to the need for alternative simvastatin formulations for pediatric use. Only limited information was recovered and none specifically related to pediatric difficulties demonstrated with the tablet formulation. The literature did not identify any administration

concerns relating to Zocor tablets in the pediatric population. Based on these data, there does not appear to be a pediatric concern with administration of the current Zocor tablets.

One safety concern is that it is much easier for the patient or caregiver to inadvertently administer more than the prescribed dose because they measure out the suspension rather than take a tablet which contains the exact dose. This safety objection could be reduced by providing information in the label advising the use of an accurate measuring device instead of a household teaspoon. Of note, in the FDA 3/21/14 response to the sponsor's question: "Question 16: Does the Agency agree that there is no need to supply a dosing utensil with the drug product?", FDA/DMEPA responded: "Yes, we agree that there is no need to supply a dosing utensil with the drug product." The sponsor's rationale was that the minimum recommended dose is 5 mg, which equates to 1.25 mL of Simvastatin Oral Suspension, 20 mg/5 mL. Dosing utensils that accurately deliver 0.25 mL increments for oral liquid products are commercially available.

The active pharmaceutical ingredient (API), Simvastatin, USP, is sourced from (b) (4)

Regulatory

On January 06, 2014, the Division of Metabolism and Endocrinology Products (DMEP) received correspondence from Perrigo Pharmaceuticals/Rosemont Pharmaceuticals requesting a meeting to discuss plans to submit a 505(b)(2) NDA for simvastatin oral suspension. The Division denied the meeting but sent written responses to the applicant's questions on March 21, 2014. The Division stated additional clinical studies would not likely be required provided adequate data were submitted to bridge the test product, simvastatin oral suspension, and the listed drug Zocor® (simvastatin oral tablets). Whether additional clinical trials for safety and/or efficacy would be required would also depend on the division's review of the nonclinical and clinical data, as well as the division's review of the applicant's initial Pediatric Study Plan. Required chemistry and manufacturing studies and reports were also described.

On February 24, 2014, DMEP received a pre-NDA briefing package for Rosemont's proposed 505(b)(2) NDA application for Simvastatin Oral Suspension. The Division sent written responses to the applicant's questions on March 21, 2014. We stated that based on the information provided, the proposed approach for establishing bioequivalence is appropriate.

On June 22, 2015, Paddock Laboratories, LLC, a Perrigo Company (Paddock) on behalf of Rosemont Pharmaceuticals Ltd., submitted a 505(b)(2) NDA application for simvastatin oral suspension in dosage strengths of 20 mg/5 mL and 40 mg/5 mL. The proposed labeling for safety and efficacy, dosing and duration of dosing for Simvastatin Oral Suspension is the same as the approved labeling for ZOCOR® (simvastatin) Tablets. Information pertaining to clinical studies performed by Rosemont Pharmaceuticals, Ltd. in support of this NDA application has also been added to the proposed insert. The prescribing

information includes additional instructions that patients should be prescribed the 40 mg/5 mL strength product for doses of 40 mg or greater per day. Additional minor differences in the proposed labeling and the reference drug labeling include differences in the product name, strength, dosage form, formulation, and manufacturer. The reference listed product is Zocor® manufactured by Merck Sharp & Dohme Corp. approved under NDA 19766 in 1991. I have provided comments regarding some of these labeling changes in the labeling section of this review.

Biopharmaceutical Studies Submitted to NDA 206679

Rosemont conducted a fasted comparative bioequivalence (BE) study and a study of food effect on bioavailability (BA) in support of the US application.

- **Protocol PRG-NY-14-010:** an open-label, randomized, reference replicate, single oral dose, two-treatment, three period, three-way crossover relative bioavailability study of 80 mg Zocor® Tablets versus 10 mL of Simvastatin Oral Suspension, 40 mg/5 mL in healthy adults under fasted conditions.

- **Protocol PRG-NY-14-011:** an open-label, randomized, single oral dose, one treatment, two-period, two-way crossover food effect study of 10 mL of Simvastatin Oral Suspension, 40 mg/5 mL, administered under fed versus fasted conditions in healthy adults.

These studies were reviewed in detail by Dr. Johnny Lau from the Office of Clinical Pharmacology. Please refer to his review in DARRTS (submitted 3/17/2016, Reference ID: 3904256) for a more in-depth analysis of the BE/BA studies. The conclusion from the clin-pharm team is that the data are acceptable to support approval. Due to the significant effect of food on the exposure of simvastatin suspension, the product label needs to carry the following statement:

- The recommended usual starting dose is 10 or 20 mg once a day in the evening on an empty stomach.

Rosemont also performed a BE study for the market approval in the UK and Ireland. **Protocol SC02806** was a comparative BE evaluation of Zocor® Tablets, 20 mg versus Simvastatin Oral Suspension, 20 mg/5 mL (5 mL dose). The study design was in fasted subjects with a four-period, two-sequence, replicate design that employed a single oral dose of the treatment compound (Simvastatin Oral Suspension, 20 mg/5 mL) versus the reference formulation (Zocor® Tablets, 20 mg) for fasted subjects. Marketing authorization was granted in the United Kingdom (June 4, 2010) and Ireland (August 20, 2010) for the Simvastatin Oral Suspension, 20 mg/5 mL and 40 mg/5 mL strengths developed by Rosemont Pharmaceuticals Ltd. After market authorization in 2010, (b) (4) batches of the 20 mg/5 mL and (b) (4) batches of the 40 mg/5 mL strengths have been manufactured.

Table 1: Listing of Clinical Studies Conducted by Rosemont Pharmaceuticals

Type of Study	Study Identifier	Objective(s)	Study Design and Type of Control	Test Product(s); Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
BE	PRG-NY-14-010	Relative BA of Simvastatin Oral Suspension (Test) vs. Zocor® Tablet (Reference)	open-label, balanced, randomized, reference replicate, single oral dose, two-treatment, three period, three-way crossover study for the relative BA of Simvastatin Oral Suspension, 40 mg/5 mL (10 mL or 80 mg total) vs. Zocor Tablets, 80 mg	Test Treatment: Simvastatin 40 mg/5 mL Oral Suspension; Single dose (10 mL); Oral Reference Treatment: Zocor® (Simvastatin) 80 mg Tablet; Single dose (1 tablet); Oral	42	Healthy Subjects	Single Dose
BA	PRG-NY-14-011	Food effect of Simvastatin Oral Suspension in Fed (Test) vs Fasting (Test) States	open-label, balanced, randomized, reference replicate, single oral dose, one-treatment, two period, two-way crossover, food effect study comparing 10 mL of Simvastatin Oral Suspension, 40 mg/5 mL administered under fed conditions and 10 mL Simvastatin Oral Suspension, 40 mg/5 mL administered under fasting conditions in healthy adult, male or female study participants.	Test Treatment (Fed): Simvastatin 40 mg/5 mL Oral Suspension; Single dose (10 mL); Oral Test Treatment (fasted): Simvastatin 40 mg/5 mL Oral Suspension; Single dose (10 mL); Oral	56	Healthy Subjects	Single Dose
BE	SC02806[1]	Comparative BE of Zocor® Tablets, 20 mg versus Simvastatin Oral Suspension, 20 mg/5 mL (5 mL dose) in fasted	four-period, two-sequence, replicate design to compare a single oral dose of the treatment compound (Simvastatin Oral Suspension, 20 mg/5 mL) versus the reference formulation (Zocor® Tablets, 20 mg) under fasted conditions in healthy adult, male or female study participants	Test Treatment: Simvastatin 20 mg/5 mL Oral Suspension; Single dose (5 mL); Oral Reference Treatment: Zocor® (Simvastatin) 20 mg Tablet; Single dose (1 tablet); Oral	28	Healthy Subjects	Single dose

1 This study was conducted in support of the marketed application in the UK and Ireland.

(b) (4) conducted both PRG-NY-010 and PRG-NY-011. The principal investigator was:

Sudershan Vishwanath, MD
Senior Clinical Pharmacologist – Clinical Research
(b) (4)

The BE study performed for the UK and Ireland market authorization, SC02806, was performed by (b) (4)

STUDY SUMMARIES

Protocol PRG-NY-14-010: fasted comparative bioequivalence (BE) study

An open-label, randomized, single oral dose, two-treatment, three period, three-way crossover relative bioavailability study of 80 mg Zocor® Tablets versus 10 mL of Simvastatin Oral Suspension, 40 mg/5 mL in healthy adults under fasted conditions (at least 10 hours.)

Protocol PRG-NY-14-010 was conducted by (b) (4) and is designated in their report as study number 12192/13-14. A total of 42 healthy adult men and women (age 18 – 55 years old) were enrolled in the study but 36 subjects completed all three periods; the BE data were generated from these 36 subjects. However, reference variability was based on data from 38 subjects who received reference drug (Zocor® Tablets) in at least two periods.

After an information request, Paddock confirmed that simvastatin tablet lot number J008788 used in Study PRG-NY-14- 010 is the same product approved in the United States and marketed as 80 mg Zocor® tablets under Merck's NDA 019766.

Pharmacokinetic measurements were taken for simvastatin and the major active form, ß-hydroxyacid simvastatin. The statistical measures of the relative bioavailability included natural and log-transformed values for AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, terminal disposition rate (λZ), and $T_{½}$.

Bioequivalence was assessed using a linear mixed effects model, which included fixed effects terms for sequence, treatment, period and a random effects term for subject (sequence). The 90% confidence intervals for the difference between Treatment T (Test) vs. Treatment R (Reference) least-squares means comparison were calculated. The Test-to-Reference difference and the confidence interval for the log-transformed parameter were exponentiated to obtain estimates of the ratio of the Test over Reference geometric means and the 90% CI for the ratio, respectively.

If 90% CIs of the ratio estimates for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within 80.00 to 125.00%, then the Test treatment would be concluded as bioequivalent to the Reference treatment. The applicant states that the results demonstrated the test and reference were bioequivalent based on the following:

- The data showed the 90% confidence intervals for AUC0-t and AUC0-∞ were (82.05, 98.79) and (81.13, 97.89), respectively.
- The point estimate of the Test/Reference geometric mean titer (GMT) ratio of 85.86% was within 80.00% to 125.00%.

Protocol PRG-NY-14-011: food effect on bioavailability (BA)
An open-label, randomized, single oral dose, one treatment, two-period, two-way crossover food effect study of 10 mL of Simvastatin Oral Suspension, 40 mg/5 mL, administered under fed versus fasted conditions in healthy adults.

The planned sample size was for 56 subjects. A total of 70 healthy adult subjects (age 18 – 55 years old, both genders) were screened and 62 were deemed eligible. Of those, 56 subjects were continued for dosing in Period I with six replacement subjects, if needed. The plasma samples from 56 subjects were evaluated.

Pharmacokinetic measurements were taken for simvastatin and the major active form, ß-hydroxyacid. The statistical measures of the relative bioavailability included natural and log-transformed values for AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, terminal disposition rate (λZ), and $T_{½}$.

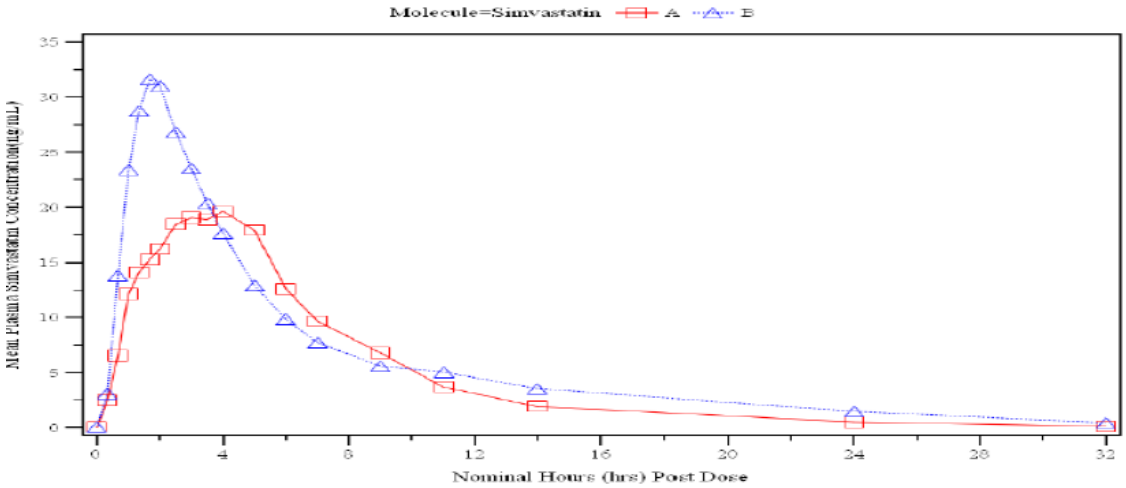
The food effect was assessed using a linear mixed effects model, which included fixed effects terms for sequence, treatment, period and a random effects term for subject (sequence). The 90% confidence intervals for the difference between Test Treatment T (fed) vs. Reference Treatment R (fasted) least-squares means comparison were calculated for log-transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}. The Test-to-Reference difference and the confidence interval for the log-transformed parameter were exponentiated to obtain estimates of the ratio of the Test over Reference geometric means and the 90% CI for the ratio, respectively. If 90% CIs of the ratio estimates for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within 80.00 to 125.00%, then the Test treatment would be concluded that there is no food effect.

The applicant states that the results demonstrated a food effect.

- For simvastatin, there was a 26.35% decrease in C_{max}, a 16.22% decrease in AUC_{0-t}, and a 17.45% decrease in $AUC_{0-\infty}$ for the fed vs. fasted states. With respect to T_{max}, the fed state was 3.50 hours as compared to 1.67 hours for the fasted state.
- For simvastatin ß-hydroxyacid, there was a 73.24% increase in C_{max}, a 49.17% increase in AUC_{0-t}, and a 43.76% increase in $AUC_{0-\infty}$ for the fed vs. fasted states. With respect to T_{max}, the fed state was 5.50 hours as compared to 4.00 hours for the fasted state.

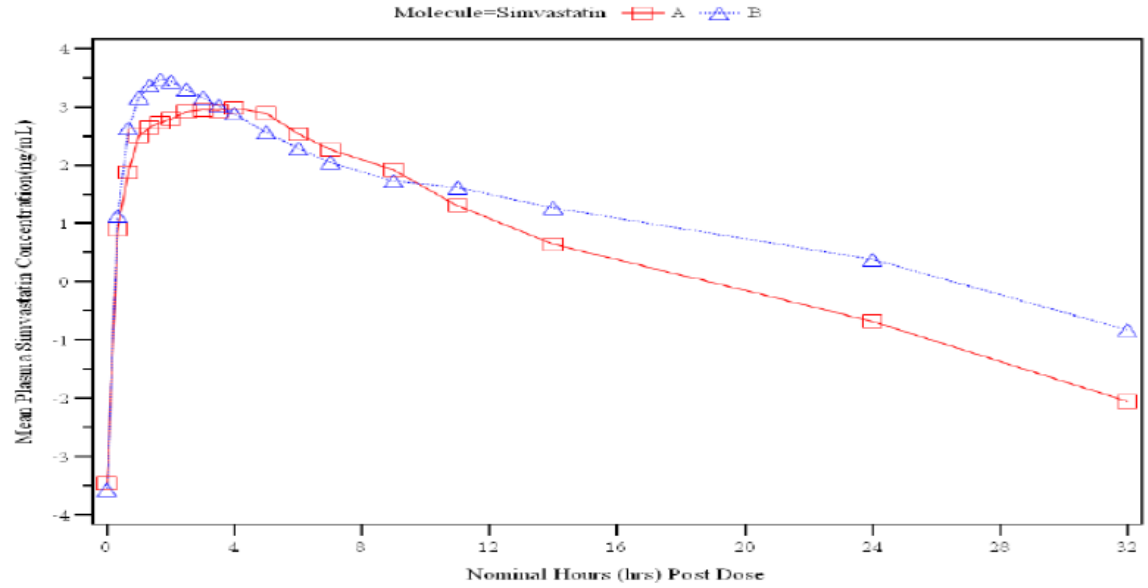
The mean plasma levels for simvastatin over time are summarized in the following two figures for linear scale (Figure 1) and log linear scale (Figure 2). Note that Form A = fed state and Form B = fasted state.

Figure 1: Simvastatin Mean Plasma Levels (Linear Scale) vs. Time: Fed vs. Fasted Conditions



Form A = fed state; Form B = fasted state
Source: Applicant's Figure 5.3.1.1-1

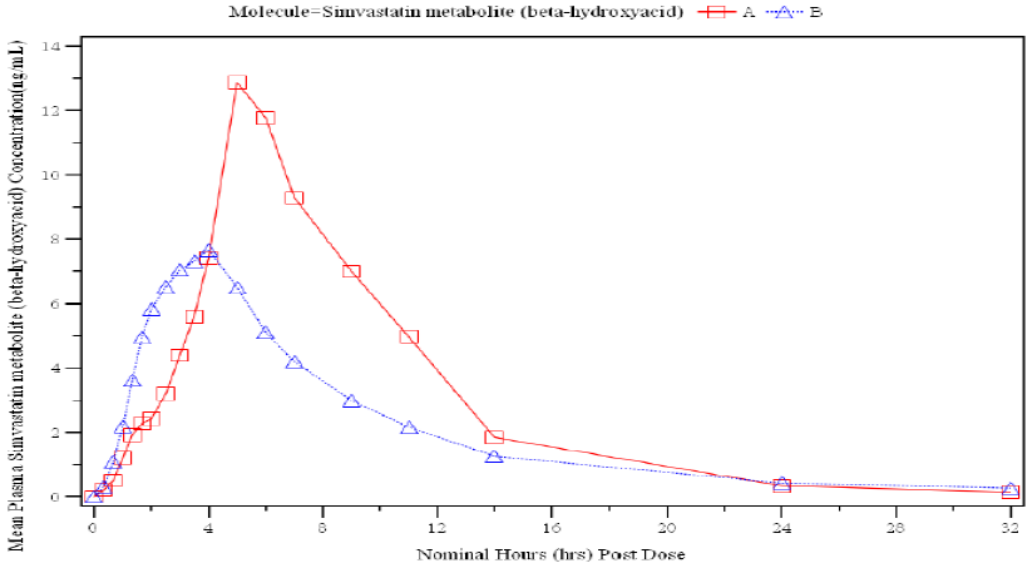
Figure 2: Simvastatin Mean Plasma Levels (Log Linear Scale) vs. Time: Fed vs. Fasted Conditions



Form A = fed state; Form B = fasted state
Source: Applicant's Figure 5.3.1.1-2

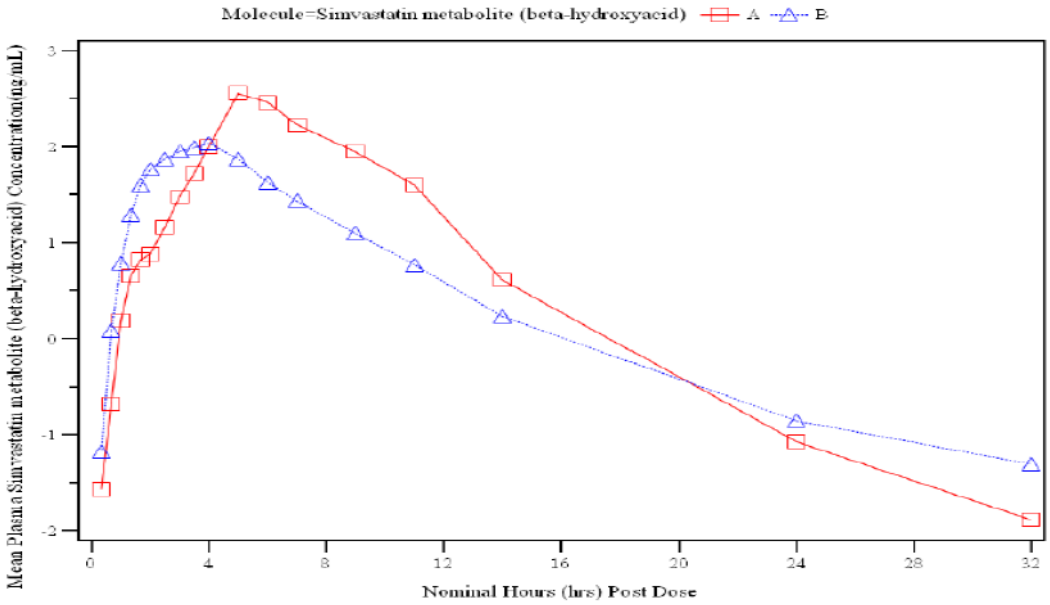
The mean plasma levels for simvastatin ß-hydroxyacid over time are summarized in the following two figures for linear scale (Figure 3) and log linear scale (Figure 4). Note that Form A = fed state and Form B = fasted state.

Figure 3: Simvastatin ß-hydroxyacid Mean Plasma Levels (Linear Scale) vs. Time: Fed vs. Fasted Conditions



Source: Applicant's Figure 5.3.1.1-3

Figure 4: Simvastatin ß-hydroxyacid Mean Plasma Levels (Log Linear Scale) vs. Time: Fed vs. Fasted Conditions



Source: Applicant's Figure 5.3.1.1-4

The applicant notes that there have been reports of food effects with simvastatin and high fat meals. The applicant comments that a food effect was documented for a fixed dose combination (FDC) product comprised of sitagliptin and simvastatin in ratios of 100 mg sitagliptin with 10, 20, or 40 mg simvastatin. The product is marketed in Australia under

the trade names Juvicor®, Xelezor®, or Tesozor®; the market application sponsor is Merck Sharpe & Dohme (Australia) Pty Ltd. A 2-way crossover food-effect study compared the relative bioavailability of the sitagliptin/ simvastatin (100 mg/80 mg FDC) tablet under both fasted and fed (Treatments A and B, respectively) in 32 healthy adult subjects. A high-fat meal (~845 Kcal, 59% fat) increased the C_{max} of simvastatin and simvastatin acid by 20% and 116%, respectively, compared to the fasted state.

The AusPAR (Australian Product Assessment Report) questioned whether the food effect might pose an additional risk in the setting of concomitant use with CYP3A4 inhibitors. The sponsor noted the safety provisions in the current prescribing information for Zocor® Tablets have precautionary statements and dosage limitations in particular situations of concomitant use of other medications that are known to be potent CYP 3A4 inhibitors. The labelling for the FDC product was revised to contain similar language.

For this submission, the applicant proposes that the labeling for Simvastatin Oral Suspension will state the results of the food effect study but surmise that these differences do not impact the safety or efficacy of the product and may be taken without regard to food.

Protocol SC02806

Protocol SC02806 was conducted by (b) (4) in 2007 as part of the registration of Simvastatin Oral Suspension in the (b) (4) . The study was designed as a two-way crossover to compare the bioavailability (BA) of a 20 mg dose of Simvastatin Oral Suspension versus a 20 mg dose of Zocor Tablets under fasted conditions. A total of 27 healthy adult men and women (age 18 – 50 years old) were enrolled and randomized; 26 subjects completed.

Pharmacokinetic measurements were taken for simvastatin and the major active form, ß-hydroxyacid simvastatin. The statistical measures of the relative bioavailability included natural and log-transformed values for AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, terminal disposition rate (λZ), mean residence time (MRT), and $T_{½}$.

The applicant states that the results demonstrated the test and reference were bioequivalent based on the following:

- With respect to the C_{max} for simvastatin (parent), rate of simvastatin absorption was shown bioequivalent based on the log-transformed data of the 90% confidence interval (89.12% - 113.04%) that met the acceptance limits of 80% to 125%. The 90% confidence interval for C_{max} for the active metabolite ß-hydroxyacid acid was 92.22% - 120.43%.
- With respect to AUC_{0-t} and $AUC_{0-\infty}$ for simvastatin, bioequivalence was shown based on the log-transformed data of the 90% CI for simvastatin showed AUC_{0-t} and $AUC_{0-\infty}$ ranges of 82.84% - 107.46% and 82.52% - 107.14%, respectively. These met the acceptance limits of 80% to 125%. The 90% confidence intervals for ß-

hydroxyacid simvastatin showed AUC_{0-t} and $AUC_{0-\infty}$ ranges were 85.50% - 123.42% and 89.25% - 113.00%, respectively.

Clinical-Pharmacology Team Issues in 74-day letter:

- "We acknowledge the previous response in the letter dated March 21, 2014 for NDA 206-679 regarding the proposed approach to establish bioequivalence for simvastatin oral suspension. Upon further consideration, however, we have concern that the scaled bioequivalence approach used in the pivotal study (PRG-NY-14-010) to assess bioequivalence between the test simvastatin oral suspension and the reference ZOCOR tablet may not be consistent with the approach used for other approved simvastatin products to assess bioequivalence. The use of scaled bioequivalence approach to establish bioequivalence for simvastatin oral suspension will be a review issue."

Clinical-Pharmacology Team Summary and Recommendations
(Source: Review in DARRTS, submitted 3/17/2016, Reference ID: 3904256)

The sponsor submitted the results of 3 clinical pharmacology studies (PRG-NY-14-010, PRG-NY-14-011, and SC02806) to support NDA 206-679. Study PRG-NY-14-010 assessed the bioequivalence between 80 mg simvastatin oral suspension (10 mL of 40 mg/5mL) and 80 mg simvastatin tablet (Zocor) under fasting. Study PRG-NY-14-011 assessed the relative bioavailability of 80 mg simvastatin suspension (10 mL of 40 mg/5mL) in the presence of a high fat meal and under fasting. Study SC02806 assessed the relative bioavailability between 20 mg simvastatin oral suspension (20 mg/5 mL) and 20 mg Zocor tablet under fasting. The sponsor requested a biowaiver for the 20 mg/5 mL simvastatin oral suspension. See Biopharmaceutics reviewer's review regarding the request of biowaiver.

Results of simvastatin C_{max} and AUCs indicate that 10 mL of 40 mg/5 mL simvastatin oral suspension is bioequivalent to the 80 mg simvastatin tablet (Zocor) under fasting via the reference scaled bioequivalence approach. Results of simvastatin acid C_{max} indicate that 10 mL of 40 mg/5 mL simvastatin oral suspension is not equivalent to the 80 mg simvastatin tablet (Zocor) under fasting via the reference scaled bioequivalence approach. However, results of simvastatin acid AUCs indicate that 10 mL of 40 mg/5 mL simvastatin oral suspension is equivalent to the 80 mg simvastatin tablet (Zocor) under fasting condition via the reference scaled bioequivalence approach. Simvastatin (parent drug) pharmacokinetic data are primary to assess bioequivalence between simvastatin suspension and 80 mg Zocor tablet, whereas simvastatin acid (metabolite) pharmacokinetic data are considered supportive evidence.

The submission batches for the simvastatin suspension were manufactured at full scale-up (commercial) size. There are no differences between the formulation of the submission batches, clinical batch, and proposed commercial formulation. The 80 mg Zocor tablets

used in Study PRG-NY-14-010 is the United States-approved and marketed product. Also, the Orange Book lists 80 mg Zocor as the reference listed drug.

Study PRG-NY-14-011 shows that a high fat meal affects the exposure of simvastatin suspension. Simvastatin C_{max} geometric mean ratio under fed and fasting conditions as well as that of simvastatin $AUC_{0-\infty}$ decreased 26.4% and 17.5%, respectively. Simvastatin acid C_{max} geometric mean ratio under fed and fasting conditions as well as that of simvastatin acid $AUC_{0-\infty}$ increased 73.2% and 43.8%, respectively.

Recommendations: The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 206-679's Clinical Pharmacology data submitted on June 22, 2015, October 6, 2015, and February 26, 2016. The data are acceptable to support approval. Due to the significant effect of food on the exposure of simvastatin suspension, the product label needs to carry the following statement (language in italics is different from Zocor label):

- The recommended usual starting dose is 10 or 20 mg once a day in the evening *on an empty stomach*.

SAFETY

Protocol PRG-NY-14-010 (Comparative BE – Fasted State)

Drug Exposure
Period I:
In total, 42 participants were administered the study formulations, so that 14 participants received a single dose of Simvastatin Oral Suspension 40mg/5mL and 28 participants received a single dose of Zocor® (Simvastatin) 80 mg tablets.

Period II:
In total, 39 participants were administered the study formulations, so that 13 participants received a single dose of Simvastatin Oral Suspension 40mg/5mL and 26 participants received a single dose of Zocor® (Simvastatin) 80 mg tablets.

Period III:
In total, 37 participants were administered the study formulations, so that 10 participants received a single dose of Simvastatin Oral Suspension 40mg/5mL and 27 participants received a single dose of Zocor® (Simvastatin) 80 mg tablets.

Three adverse events (AEs) occurred in two participants. Of these three AEs, two were reported in Period II (restlessness & general body pain in participant 41), and one was observed during the post-clinical assessment (eosinophil count increased in participant 03). All AEs were considered mild in severity. Of the three AEs, two were judged to be unlikely related to the study drug (eosinophil count increased in participant 03 and

restlessness in participant 41) and the remaining one AE was judged possibly related to the study drug (general body pain in participant 41) by the Medical Investigator. The outcomes of all AEs were resolved with no sequelae.

- Participant 03: eosinophil count increased (14.5%, Reference range: 1.0-8.0%) during post-clinical assessment performed on 19 Jan 2014. As per repeat lab test on 24 Jan 2014, the abnormal laboratory value was not within reference range (14.2%). When a repeat lab test was conducted on 31 Jan 2014, the abnormal laboratory value was not within reference range (11.2%). The abnormal laboratory value was considered to be clinically non-significant by the Medical Investigator; this reviewer concurs. The event was judged as mild in severity. The outcome of the event was categorized as resolved with no sequelae and considered as unlikely related to the study drug by the Medical Investigator.

- Participant 41: experienced restlessness in Period II on 08 Jan 2014 at 14:20 hours (dosed at 07:12 hours on 08 Jan 2014). He was treated with a single dose of Diazepam 10 mg (by injection) on 08 Jan 2014 at 15:23 hrs. The event resolved completely without any sequelae as reported on 08 Jan 2014 at 18:00 hours. The event was judged as mild in severity and considered as unlikely related to study drug by the Medical Investigator.

- Participant 41: experienced general body pain in Period II on 08 Jan 2014 at 23:40 hours (dosed at 07:12 hours on 08 Jan 2014). He was treated with a single dose of Combiflam725 mg (paracetamol 325mg + ibuprofen 400mg), (by tablet) on 08 Jan 2014 at 23:50 hrs. The event resolved completely without any sequelae as reported on 09 Jan 2014 at 06:00 hours. The event was judged as mild in severity and considered as possibly related to the study drug by the Medical Investigator.

MO Comment: There are no worrisome safety signals or trends reported in this study.

Protocol PRG-NY-14-011 (Comparative BA – Food-Effect)

Drug Exposure
Period I:
In total, 56 participants were administered the study formulations, so that 28 participants received a single dose of Simvastatin Oral Suspension 40mg/5mL in Test Treatment (Fed State) and 28 participants received a single dose of Simvastatin Oral Suspension 40mg/5mL in Reference Treatment (Fasting State).

Period II:
In total, 52 participants were administered the study formulations, so that 25 participants received a single dose of Simvastatin Oral Suspension 40mg/5mL in Test Treatment (Fed State) and 27 participants received a single dose of Simvastatin Oral Suspension 40mg/5mL in Reference Treatment (Fasting State).

Three AEs occurred in two participants. Of these three, one AE was reported in Period I (headache in participant 21) and two were observed during post-clinical assessment (ALT

and GGT increased in participant 16). All AEs were considered mild in severity. All were judged as possibly related to the study drug and all resolved with no sequelae.

- Participant 16: ALT increased (93 IU/L, Reference range: 17 - 63 IU/L) during post-clinical assessment performed on 21 Jan 2014. As per repeat lab test on 27 Jan 2014, the abnormal laboratory value was within reference range (48 IU/L). The event was judged as mild in severity. The outcome of event was categorized as resolved with no sequelae and considered as possibly related to the study drug by the Medical Investigator.
- Participant 16: GGT increased (95 IU/L, Reference range: 7 - 64 IU/L) during post-clinical assessment performed on 21 Jan 2014. As per repeat lab test on 27 Jan 2014, the abnormal laboratory value was not within reference range (74 IU/L). The Medical Investigator considered the abnormal laboratory value clinically insignificant. The event was judged as mild in severity. The outcome of event was categorized as resolved with no sequelae and considered as possibly related to the study drug by the Medical Investigator.
- Participant 21: experienced a headache in Period I on 10 Jan 2014 at 11:00 hours (dosed at 08:06 hours on 10 Jan 2014). He was treated with a single dose of Paracetamol 500 mg tablet on 10 Jan 2014 at 14:16 hrs. The event resolved completely without any sequelae as reported on 10 Jan 2014 at 17:00 hours. The event was judged as mild in severity and considered as possibly related to the study drug by the Medical Investigator.

MO Comment: There are no worrisome safety signals or trends reported in this study.

Protocol SC02806 (Comparative BE – Fasted State) for UK Approval

Exposure
In this four period, single dose study, 26 volunteers who completed the study received both treatments twice, which consisted of 20 mg simvastatin in each period. Total individual drug exposure over the whole study was 80 mg simvastatin.

According to the adverse event listings from this submission, four AEs occurred in three participants: three were rated mild and one was moderate. The three mild AEs were comprised of elevated AST and ALT and elevated bilirubin level at post study, which the Investigator considered to be probably or possibly related to study medication. All resolved without treatment. Laboratory datasets were not submitted for this study so the values of the ALT/AST elevations are not provided. The fourth AE was dysmenorrhea which was moderate in intensity, was treated with diclofenac, and was not believed to be related to study drug.

MO Comment: There are no worrisome safety signals or trends reported in this study.

Response to FDA's Query Relating to the Marketing Experiences with Simvastatin Oral Suspension Outside the United States

Simvastatin Oral Suspension is approved for marketing in the U.K. and Ireland for Rosemont Pharmaceuticals LLC.[1] The applicant was asked to provide information on the adverse events seen in this postmarketing database.[2] This information was provided in the iPSP under IND (b) (4) (Dec 2014) and the Pre-NDA 206679 briefing package (attachment 6, Feb 2014).

In the pre-NDA briefing package (Feb 2014, pages 867-871), a summary of adverse event reports for Rosemont's marketed Simvastatin Oral Suspension was provided. The most common adverse reactions reported pertaining to Rosemont's Simvastatin Oral Suspension were headache, nausea, insomnia, diarrhea, memory impairment, depression/emotional distress, and dizziness/vertigo. I saw one case of drug administration too long (verbatim)/incorrect drug administration duration (preferred term) but no cases specifically describing an overdose error.

MO Safety Conclusion: 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.

AUDITS

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection (see review in DARRTS, dated 8/27/15, ID # 3811986). OSIS recently inspected the clinical site of (b) (4) and the inspectional outcome from the inspection was classified as No Action Indicated (NAI).

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[1] The Marketing Authorization Application for Simvastatin Oral Suspension was submitted by Rosemont to the UK Regulatory Authority (MHRA) in May 2008. The sponsor states that marketing authorization was granted in the United Kingdom (June 4, 2010) and Ireland (August 20, 2010) for the Simvastatin Oral Suspension, 20 mg/5 mL and 40 mg/5 mL strengths developed by Rosemont Pharmaceuticals Ltd. After market authorization in 2010, 46 batches of the 20 mg/5 mL and 69 batches of the 40 mg/5 mL strengths have been manufactured.

[2] Adverse event data for Simvastatin Oral Suspension is available prior to 2010 because Simvastatin Oral Suspension 20 mg/5 mL and 40 mg/5 mL were marketed by Rosemont in the UK prior to 2010. The European and UK law at that time allowed unlicensed medicines to be made available where there is no licensed drug product available but there is a medical need for the product (as per the UK Medicines Act 1968 (as amended), European Directive 2001/83/EC). Rosemont marketed Simvastatin Oral Suspension under the UK Regulatory Authority's (MHRA) "Specials" Manufacturers License No. 0427/01 from mid-2006 until the licensed product launched in 2012.

In addition, OSIS recommends accepting data without an on-site inspection of the analytical site of [redacted]. Although the last inspection was classified as a VAI, based on the nature of the findings from the inspection and OSIS' recommendation to the review division, an inspection of the analytical site will not be needed at this time.

CMC/QUALITY

There were multiple issues at the filing meeting (August 2015) that were conveyed to the applicant regarding the need for more detailed dissolution data, antimicrobial effectiveness testing, and, as non-sterile aqueous drug products may potentially be contaminated with organisms in the Burkholderia cepacia complex (BCC), test methods and acceptance criteria to demonstrate the drug product is free of BCC.

The CMC/Quality final assessment is as follows:

- The recommendation from the Office of Pharmaceutical Quality (including the manufacturing inspection recommendation) is for approval. There is no unresolved deficiency.
- Labeling comments will be finalized during the multi-disciplinary review managed by OND. However, the following recommendations were made in the review: To reflect the conditions used in the analytical methods for Particle Size Distribution and Resuspendability, labeling should include the instruction "Shake well for at least 20 seconds". Based on stability data, labeling should include the instruction "Protect from heat".
- There appear to be no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history, and relevant experience. The facilities are determined acceptable to support approval of NDA 206679.

PHARMACOLOGY/TOXICOLOGY

One of the issues at the filing meeting (August 2015) that was conveyed to the applicant was that the drug product contains at least one novel excipient (Strawberry Flavouring [redacted]) that has not been used in any approved drug product in the United States. Because no nonclinical toxicology studies were provided to qualify this novel excipient or potential drug-related impurities, drug product safety will be dependent on review of the available toxicology and quality data and literature review provided.

The applicant responded on 11/16/2015 that Strawberry Flavouring [redacted] contains [redacted], however the identity and amount of the remaining ingredients is proprietary information. As the applicant does not have access to the individual ingredients contained in the formulation, for inquiries pertaining to the strawberry flavor, the Agency should contact [redacted]

Dr. Lee Elmore confirmed that he had the needed information from the Drug Master File (DMF). In the absence of any substantial safety concerns identified, Pharmacology/Toxicology recommends Simvastatin oral suspension for approval. Please refer to the Pharm/Tox final assessment (entered into DARRTS 3/22/2016; Reference ID: 3906236).

FINANCIAL DISCLOSURE

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

The applicant has a similar label to that of the reference product, Zocor ®, with the following exceptions:

- Changed the name from ZOCOR to SIMVASTATIN ORAL SUSPENSION
- References to ZOCOR are changed to simvastatin throughout the label
- Dosage and Administration section
    - Added "Shake bottle well before using"
    - Added "Recommended to use SIMVASTATIN ORAL SUSPENSION 40 mg/5 mL for dosages greater than or equal to 40 mg."

MO Comment: The clin-pharm team recommends that the dosage and administration section clarify that simvastatin suspension should be taken without food (see italics). I have no objection to this addition.

Recommended usual starting dose is 10 or 20 mg once a day in the evening *on an empty stomach*. (2.1)

If approved, consider adding more detailed dosing information to aid in preventing inadvertent overdosing. Based on example from Promethazine HCl, Phenylephrine HCl and Codeine Phosphate Syrup:

Patients should be advised to measure SIMVASTATIN ORAL SUSPENSION with an accurate measuring device. A household teaspoon is not an accurate measuring device and could lead to overdosage, (b) (4) *A pharmacist can recommend an appropriate measuring device and can provide instructions for measuring the correct dose.*

This language could also be added to the (b) (4) *and to section 17: Patient Counseling Information. Simvastatin does not have a Patient Package Insert (PPI), otherwise would also add similar language to the PPI.*

- Dosage Forms and Strengths section

- Changed Tablets:" 5 mg; 10 mg; 20 mg; 40 mg; 80 mg" to "Oral Suspension: 20 mg/5 mL and 40 mg/5 mL" in highlight section
- Changed tablet description to suspension description:
  - "SIMVASTATIN ORAL SUSPENSION 20 mg/5 mL is an off white to pinkish orange suspension with a strawberry flavor."
  - "SIMVASTATIN ORAL SUSPENSION 40 mg/5 mL is an off white to pinkish orange suspension with a strawberry flavor."

- Section 11: Description
  - Changed FROM "Tablets ZOCOR for oral administration contain either 5 mg, 10 mg, 20 mg, 40 mg or 80 mg of simvastatin and the following inactive ingredients: ascorbic acid, citric acid, hydroxypropyl cellulose, hypromellose, iron oxides, lactose, magnesium stearate, microcrystalline cellulose, starch, talc, and titanium dioxide. Butylated hydroxyanisole is added as a preservative." TO "Each 5 mL dose of SIMVASTATIN ORAL SUSPENSION contains either 20 or 40 mg of simvastatin and the following inactive ingredients: acesulfame potassium, carboxymethylcellulose sodium, citric acid monohydrate, ethylparaben, magnesium aluminum silicate, methylparaben, propylene glycol, propylparaben, simethicone emulsion, sodium lauryl sulfate, sodium phosphate, diabasic, anhydrous, strawberry flavor and water."
- Section 12.3 Pharmacokinetics
  - (b) (4) [redacted] "
  - Added "In a food effect study for SIMVASTATIN ORAL SUSPENSION, subjects who ate a high fat meal (~540 Kcal, 56% fat) demonstrated a (b) (4)% decrease in simvastatin $AUC_{0-\infty}$ and a (b) (4)% increase in ß-hydroxyacid simvastatin $AUC_{0-\infty}$, (b) (4) [redacted] respectively, beyond what was observed in the fasted state. (b) (4) [redacted] "
  - Added "In a study of 12 healthy volunteers, simvastatin at the 80-mg dose had no effect on the metabolism of the probe cytochrome P450 isoform 3A4 (CYP3A4) substrates midazolam and erythromycin. This indicates that simvastatin is not an inhibitor of CYP3A4, and, therefore, is not expected to affect the plasma levels of other drugs metabolized by CYP3A4."

MO comment: This type of information regarding the bioequivalence study is not usually included; I recommend deleting this. The food effect study results may be included if the results of this study will affect labeling, for example, if the suspension should be taken in the fasted state. I will defer section 12.3 to the clin-pharm team.

- Section 16 How Supplied/Storage and Handling
    - Change information as relevant for suspension

According to the FDA Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations for Zocor/simvastatin 5mg, 10 mg, 20 mg, 40 mg and 80 mg:

- Patent Data: There are no unexpired patents for this product in the Orange Book Database.
- Exclusivity Data: There is no unexpired exclusivity for this product.

DRUG PRODUCT NAME

The tradename of Simvastatin Oral Suspension was submitted by the applicant. No proprietary name review is necessary because simvastatin is not a proprietary name.

PEDIATRIC STUDY REQUIREMENTS

The applicant requested a full pediatric waiver for simvastatin oral suspension based on the following justification:

- The use of simvastatin for the treatment of pediatric patients for (1) Reduction in Risk of CHD Mortality and Cardiovascular Events; (2) Hyperlipidemia; and (3) Adolescent Patients with Heterozygous Familial Hypercholesterolemia (HeFH): (1) does not represent a meaningful therapeutic over existing therapies for pediatric patients, and (2) is not likely to be used in a substantial number of pediatric patients.
- The review for the waiver request met the statutory criteria based upon simvastatin's existing indication for the treatment of adolescents (10 to17 years of age) with the congenital lipid anomaly HeFH (heterozygous familial hypercholesterolemia).
- The FDA has determined that other simvastatin drug products met the criteria for a full waiver under PREA. For example both SIMCOR® (niacin extended-release/ simvastatin) and JUVISYNC® (simavastatin/sitagliptin) were granted PREA waivers in 2008 and 2011, respectively. FDA has also determined that other statin drug products met the criteria for a full waiver under PREA, such as Liptruzet® (atorvastatin/ezetimibe) and Livalo® (pitavastatin), which received waivers in 2013 and 2009, respectively.

The initial Pediatric Study Plan (iPSP) was submitted 08 December 2014 (PIND Number (b) (4)). A Pre-IND Acknowledgement Advice Letter was received 17 February 2015; the agreed iPSP was submitted 02 March 2015. This plan was reviewed by PeRC on 2/17/2016 and found to be acceptable.

RECOMMENDATION

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) concludes that the data are acceptable to support approval. Due to the significant effect of food on the exposure of simvastatin suspension, they recommend that the product label clarify that simvastatin suspension should be taken without food.

Given the clin-pharm team's assessment that simvastatin oral suspension is bioequivalent to Zocor®, I agree with approval, with label changes to take without food. The review of the simvastatin oral suspension safety data does not reveal any new safety issues. I recommend adding more detailed dosing information to aid in preventing inadvertent overdosing. Proposed label changes:

Patients should be advised to measure SIMVASTATIN ORAL SUSPENSION with an accurate measuring device. A household teaspoon is not an accurate measuring device and could lead to overdosage, (b) (4) A pharmacist can recommend an appropriate measuring device and can provide instructions for measuring the correct dose.

This language could also be added to the (b) (4) and to section 17: Patient Counseling Information. Simvastatin does not have a Patient Package Insert (PPI), otherwise would also add similar language to the PPI.

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

/s/

EILEEN M CRAIG
04/06/2016

JAMES P SMITH
04/08/2016

CLINICAL FILING CHECKLIST FOR NDA 206679

NDA Number: 206679 | **Applicant: Rosemont Pharmaceuticals, Ltd** | **Stamp Date: 6/22/2015**

IND # (b) (4)

Drug Name: Simvastatin oral suspension 20 mg/5 mL and 40 mg/5 mL | **NDA/BLA Type:505(b)(2)**

The network location is:

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Receipt date: 6/22/15
Filing meeting: Aug 5, 2015 1-2p 22:3266
Filing date: August 21, 2015
74 day letter: Sept 4, 2015
Mid cycle Meeting: Nov 19, 2015 10-11a, 22:3201
Wrap-up Meeting: Mar 16, 2016, 10-11a 22:3266
Complete primary review: Mar 16, 2016
Complete secondary review Mar 23, 2016
Send labeling to sponsor: ~Mar 25, 2016
CDTL review complete: Apr 1, 2016
PDUFA goal date: Apr 22, 2016

Biopharmaceutics Reviewer: John Duan CDER/ONDQA
Clinical Pharmacology Reviewer: Johnny Lau/Jaya Vaidyanathan
Marketing and Advertising Professional Reviewer: Ankur Kalola CDER/OPDP/DPP/PRG2
Marketing and Advertising Regulatory Project Manager: Olga Salis CDER/OMP/DDMAC
Non-Clinical Reviewer: Lee Elmore/Dave Carlson
MA - Professional Secondary Reviewer: Melinda McLawhorn CDER/OPDP/DPP/PRG2
Product Quality Reviewer: Suong Tran/ Anika Lalmansingh
Statistics: TBD
Regulatory Project Manager: Richard Whitehead

Indications:

1 INDICATIONS AND USAGE

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is indicated as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate. In patients with coronary heart disease (CHD) or at high risk of CHD, SIMVASTATIN ORAL SUSPENSION can be started simultaneously with diet.

1.1 Reductions in Risk of CHD Mortality and Cardiovascular Events

In patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, SIMVASTATIN ORAL SUSPENSION is indicated to:

- Reduce the risk of total mortality by reducing CHD deaths.
- Reduce the risk of non-fatal myocardial infarction and stroke.
- Reduce the need for coronary and non-coronary revascularization procedures.

1.2 Hyperlipidemia

SIMVASTATIN ORAL SUSPENSION is indicated to:

- Reduce elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), and triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hyperlipidemia (Fredrickson type IIa, heterozygous familial and nonfamilial) or mixed dyslipidemia (Fredrickson type IIb).
- Reduce elevated TG in patients with hypertriglyceridemia (Fredrickson type lV hyperlipidemia).
- Reduce elevated TG and VLDL-C in patients with primary dysbetalipoproteinemia (Fredrickson type III hyperlipidemia).
- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

1.3 Adolescent Patients with Heterozygous Familial Hypercholesterolemia (HeFH)

SIMVASTATIN ORAL SUSPENSION is indicated as an adjunct to diet to reduce total-C, LDL-C, and Apo B levels in adolescent boys and girls who are at least one year post-menarche, 10 to 17 years of age, with HeFH, if after an adequate trial of diet therapy the following findings are present:

1. LDL cholesterol remains ≥190 mg /dL; or
2. LDL cholesterol remains ≥160 mg /dL and

- There is a positive family history of premature cardiovascular disease (CVD) or
- Two or more other CVD risk factors are present in the adolescent patient.

The minimum goal of treatment in pediatric and adolescent patients is to achieve a mean LDL-C <130 mg/dL. The optimal age at which to initiate lipid-lowering therapy to decrease the risk of symptomatic adulthood CAD has not been determined.

1.4 Limitations of Use

SIMVASTATIN ORAL SUSPENSION has not been studied in conditions where the major abnormality is elevation of chylomicrons (i.e., hyperlipidemia Fredrickson types I and V).

Background:
The basis for this 505(b)(2) application is NDA 019766 for Zocor® (simvastatin, USP) Tablets, 5, 10, 20, and 40 mg strengths that were approved December 23, 1991 and the 80 mg strength that was approved as a supplement to NDA 019766 on July 10, 1998. The sponsor is Merck & Company, Inc.

The differences between the applicant's simvastatin suspension and Merck's Zocor/simvastatin are as follows:

2. Active ingredients	Simvastatin, USP	Simvastatin, USP
3. Inactive ingredients	Ascorbic acid, citric acid, hydroxypropyl cellulose, hypromellose, iron oxides, lactose, magnesium stearate, microcrystalline cellulose, starch, talc, and titanium dioxide. Butylated hydroxyanisole is added as a preservative.	Propylene Glycol, Methylparaben, Ethylparaben, Propylparaben, Magnesium Aluminum Silicate, Carboxymethylcellulose Sodium, Simethicone Emulsion, Sodium Lauryl Sulfate, Acesulfame Potassium, Citric Acid Monohydrate, Sodium Phosphate, Dibasic, Anhydrous, Strawberry Flavoring (b) (4) (b) (4) Water, USP
4. Route of administration	Oral	Oral
5. Dosage Form	Tablet (immediate release)	Suspension
6. Strength	5, 10, 20, 40, and 80[1] mg	20 mg/5 mL and 40 mg/5 mL

Rosemont Pharmaceuticals Ltd. is relying upon investigations for approval that "were not conducted by the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted." Per the Division's instructions in the March 21, 2014 letter summarizing the pre-NDA responses, the Sponsor claims that they have:
1. established that such reliance is scientifically appropriate and included data to support any aspects of the proposed drug that represent modifications to the reference listed drug;
2. established a bridge to the RLD by comparative bioavailability in both fasted and food-effect studies; and
3. that reliance on data from published studies is scientifically appropriate.

Thus, the applicant is using the Agency's previous findings of safety and efficacy for the approved reference listed drug, Zocor® (simvastatin, USP) Tablets (NDA 019766) to support the demonstrated safety and efficacy of the Simvastatin Oral Suspension.

This application also contains a safety assessment of the product that has been marketed in the United Kingdom and Ireland, specifically the bioequivalence study report for the UK and Ireland submissions and the post-marketing surveillance data summaries. Usage and post-marketing safety in pediatric study populations is also included.

Rosemont Pharmaceuticals Ltd. is requesting a waiver from the *in vivo* bioavailability study requirements for the 20 mg/5 mL strength per 21 §CFR 320.22(d)(2). The applicant

states that as the pharmacokinetics of simvastatin are demonstrated to be linear over the dose range prescribed for the proposed drug product, Rosemont considers performance of a bioequivalence study on the highest strength of Simvastatin Oral Suspension, 40 mg/5 mL, to be adequate to establish the bioequivalence of the 20 mg/5 mL strength as well.

Labeling:
In Module 1.14, the applicant submitted draft labeling electronically in MS Word, pdf, and SPL file formats. To facilitate review of this submission, side-by-side annotated comparisons of the proposed labeling to the listed drug labeling are also provided.

Risk Evaluation and Mitigation Strategy (REMS):
A risk management plan, Elements to Assure Safe Use (ETASU) and the Implementation System are not proposed.

Priority or Standard Review:
Standard review

Pediatric Waiver:
The PeRC on 18 March 2015 concurred with the plan for full waiver of the 6 pediatric waiver requests.
#1: Adolescent Patients 0-9 Years Old with Heterozygous Familial Hypercholesterolemia (HeFH)
#2: Mixed Dyslipidemia Children 0-17 Years Old (Fredrickson Type IIb)
#3: Dysbetalipoproteinemia in Children 0-17 Years Old (Fredrickson type III hyperlipidemia)
#4: Hypertriglyceridemia in Children 0-17 Years Old (Fredrickson type IV hyperlipidemia)
#5: Homozygous familial hypercholesterolemia (HoFH) in Children 0-17 Years Old
#6: Reduction in Risk of coronary heart disease (CHD) Mortality and Cardiovascular Events in Children 0-17 Years Old

Debarment Certification:
Rosemont Pharmaceuticals 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.

Financial Disclosures:
Rosemont Pharmaceuticals submitted 1 FDA 3454 forms and 2 FDA 3455 forms.
#1: (b) (6) certified that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 5a.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 5a.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(0).

#2: Form 3455: Simvastatin Oral Suspension 40mg/5ml BE fasting study, (b) (6) Protocol Number (b) (6) /086/ 13- 14: The following individuals participated in financial arrangements or holds financial interest. Of note, for all 10 individuals, handwritten on the forms was that none of the 4 financial options on the sheet were applicable. However, no further explanation or details was given of the individual's disclosable financial arrangements and interests and there was no description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests. Recommend that they submit this information.

- (b) (6)

#3: Form 3455: Simvastatin Oral Suspension 40mg/5ml BA food effect study, (b) (6) Protocol Number (b) (6) /087/ 13- 14: The following individuals participated in financial arrangements or holds financial interest. Of note, for all 10 individuals, none of the 4 financial options on the sheet were checked. In addition, no further explanation or details was given of the individual's disclosable financial arrangements and interests and there was no description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests. They will need to submit this information.

- (b) (6)

Site Inspection:

Concur with the recommendation by the clinical pharmacology team for Study PRG-NY-14-010: An open-label, randomized, single oral dose, two-treatment, three period, three-way crossover relative bioavailability study of 80 mg Zocor® Tablets versus 10 mL of Simvastatin Oral Suspension, 40 mg/5 mL in healthy adults under fasted conditions
Facility: (b) (4)

File name: Clinical Filing Checklist for NDA 206679

CLINICAL FILING CHECKLIST FOR NDA 206679

Address [redacted] (b) (4)

Clinical Investigator: Dr Sudershan Vishwanath MD;
Sponsor Representative: [redacted] (b) (4)

Potential review issues:

1. Biowaiver of lower strength formulation (20 mg/5 ml) is a review issue
2. Clin-pharm team has concerns with the food effect study results (Protocol PRG-NY-14-011)
3. Clin-pharm team has concerns with the scaled BE approach for the pivotal study. Typically this approach is only used for drugs that are highly variable, unlikely to be the case for simvastatin

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(2)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?				Zocor® (simvastatin, USP) Tablets; NDA 019766
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	X			

File name: Clinical Filing Checklist for NDA 206679

CLINICAL FILING CHECKLIST FOR NDA 206679

	Content Parameter	Yes	No	NA	Comment
15.	Describe the scientific bridge (e.g., BA/BE studies)				Rosemont conducted a fasted comparative bioequivalence (BE) study and a study of food effect on bioavailability (BA) in support of the US application. • **Protocol PRG-NY-14-010:** an open-label, randomized, reference replicate, single oral dose, two-treatment, three period, three-way crossover relative bio-availability study of 80 mg Zocor® Tablets vs 10 mL of Simvastatin Oral Suspension, 40 mg/5mL in healthy adults under fasted conditions. • **Protocol PRG-NY-14-011:** an open-label, randomized, single oral dose, one treatment, two-period, two-way crossover food effect study of 10 mL of Simvastatin Oral Suspension, 40 mg/5 mL, administered under fed versus fasted conditions in healthy adults.
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:			X	See the responses to Questions 14 and 15 for a description of the studies.
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on	X			

	Content Parameter	Yes	No	NA	Comment
	proposed draft labeling?				
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Pharm-tox information requested 3/14: A comparative bridging toxicity study has been required with other applications to address any differences between the new product and the referenced one, primarily to bridge the impurity profiles because there may be

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
					impurities that go undetected by the analytic techniques used. Potentially genotoxic impurities and degradation products may necessitate additional information and qualification. Additional safety information may be needed for any excipients that are novel or present in concentrations that exceed levels in prior approved products or established safety levels (e.g. strawberry flavoring). The strawberry flavoring is a novel excipient. Update on 8/11/2015: Pharm/Tox has confirmed that the formulation of the non-compendial excipient (flavoring agent) contained in the drug product is available for our review.
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	

CLINICAL FILING CHECKLIST FOR NDA 206679

	Content Parameter	Yes	No	NA	Comment
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			The forms are incomplete and additional information has been requested.*
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

* The company responded on 7/22/2015: "None of the clinical investigators utilized for the clinical study of Simvastatin Oral Suspension participated in financial arrangements or hold financial interest that are required to be disclosed as described in Form FDA 3455. Therefore, there is no potential bias or financial disclosure to provide. As per FDA's February 2013 Guidance for Industry "*Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosure by Clinical Investigators*," section B.1.A, to meet the requirements of 21 CFR§54.4(a), Form FDA 3454 should be submitted if there is no disclosable financial interests **or** Form FDA 3455 should be submitted if there are disclosable financial interests. Because there are no disclosable financial interests, Form FDA 3455 is not required and Paddock is withdrawing all Form FDA 3455 forms from NDA 206679."

"In summary: Paddock is withdrawing all Form FDA 3455 Disclosure: Financial Interests and Arrangements of Clinical Investigators forms submitted in NDA 206679 and resubmitting an updated Form FDA 3454 Certification: Financial Interests and Arrangements of Clinical investigators with an attachment listing all clinical investigators."

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _yes_____

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Eileen Craig 8/13/2015

Reviewing Medical Officer Date

Clinical Team Leader Date

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

/s/

EILEEN M CRAIG
08/13/2015

JAMES P SMITH
08/13/2015