

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206679Orig1s000

CHEMISTRY REVIEW(S)



QUALITY REVIEW



Recommendation:

Approval

(including the Facility Review/Manufacturing Inspection Recommendation)

NDA 206679 Review #1 Review Date (see page 6)

| | |
|--------------------------------|------------------------------|
| Drug Name/Dosage Form | simvastatin oral suspension |
| Strength | 20 mg/5 mL and 40 mg/5 mL |
| Route of Administration | oral |
| Rx/OTC Dispensed | Rx |
| Applicant | Rosemont Pharmaceuticals Ltd |

| SUBMISSION(S) REVIEWED | DOCUMENT DATE |
|------------------------|---------------|
| 0000 | 6/22/2015 |
| 0005 | 11/20/2015 |
| 0006 | 11/25/1015 |
| 0007 | 12/17/2015 |
| 0009 | 1/29/2016 |
| 0010 | 2/9/2016 |

Quality Review Team

| DISCIPLINE | REVIEWER | DIVISION/OFFICE |
|-------------------------------------|--------------------|---|
| Application Technical Lead | Suong Tran | New Drug Products I/ONDP |
| Regulatory Business Process Manager | Anika Lalmansingh | Regulatory Business Process Management I/OPRO |
| Drug Substance | Sukhayama Bain | New Drug API/ONDP |
| Drug Product | Anne Marie Russell | New Drug Products II/ONDP |
| Biopharmaceutics | Mei Ou | Biopharmaceutics/ONDP |
| Process | Derek Smith | Process Assessment II/OPF |
| Microbiology | Jonathan Swoboda | Microbiology Assessment II/OPF |
| Facility | Xiaohui Shen | Inspectional Assessment/OPF |

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | STATUS | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|--------|-----------------|--|-----------------------|---------------|
| (b) (4) | II | | (b) (4) | Adequate | 2/26/2016 | by S. Bain |
| | III | | | Sufficient information provided in NDA | | by A. Russell |
| | III | | | | | |
| | IV | | | Adequate | 9/29/2015 | |

B. Other Documents: *IND, RLD, or sister applications*

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|--|
| NDA | 19766 | Zocor (simvastatin) Tablets Listed drug relied upon |

2. CONSULTS: not applicable

Executive Summary

I. Recommendations

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.

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues: not applicable
2. Action letter language: not applicable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

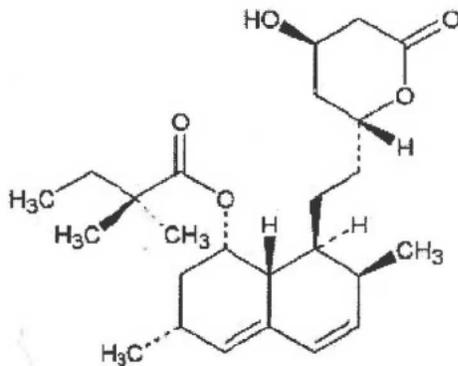
II. Summary of Quality Assessment

This is a 505(b)(2) application for a new dosage form of simvastatin, an oral suspension that relies on FDA's findings of safety and efficacy for Zocor Tablets of NDA 19766.

A. Drug Substance

Chemical Name or IUPAC Name/Structure

Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1 α ,3 α ,7 β ,8 β (2S*,4S*),-8a β]]. The empirical formula of simvastatin is C₂₅H₃₈O₅ and its molecular weight is 418.57. Its structural formula is:



DMF (b)(4) is referenced for all CMC information on the drug substance.

The drug substance is Simvastatin USP and has the BCS designation of II (poor aqueous solubility). It is a non-hygroscopic white to off white powder that is (b)(4) and (b)(4) (with a (b)(4)). It has a specific optical

rotation of 285-298 °, pH of 6.40-6.55, pKa of 13.49, and melting point of 135-138 °C. The drug substance is crystalline with one polymorph (Form I).

Information on the drug substance manufacture (including starting materials, synthesis, process, container closure, and retest period) is submitted in DMF (b) (4).

The regulatory drug substance specification in the NDA is consistent with the drug substance specification in DMF (b) (4), both found adequate for this type of active ingredient based on the supporting release and stability data. The specification is based on the USP monograph with the addition of Residual Solvents, (b) (4) and Particle Size.

B. Drug Product

The product is an immediate release oral suspension with two concentrations/strengths: 20 mg/5 mL and 40 mg/5 mL. It is an off-white to pinkish-orange suspension with a strawberry flavor.

The formulation includes a (b) (4) (propylene glycol), a (b) (4) (acesulfame potassium), (b) (4) (methylparaben, ethylparaben, and propylparaben), a strawberry flavoring, and is buffered for pH (6.4 – 7.2).

Excipients are acesulfame potassium, carboxymethylcellulose sodium, citric acid monohydrate, ethylparaben, magnesium aluminum silicate, methylparaben, propylene glycol, propylparaben, simethicone emulsion, sodium lauryl sulfate, sodium phosphate, dibasic, anhydrous, strawberry flavor and water. The strawberry flavor is a novel excipient, with CMC information in DMF (b) (4). Refer to the Pharmacology Toxicology review of the safety information on the strawberry flavor excipient.

The product manufacturing process consists of (b) (4) all the ingredients in a specific order to achieve the desired uniform suspension product (e.g., viscosity, resuspendability, particle size distribution, and drug content) and filling into bottles.

The regulatory drug product specification is adequate based on the supporting release and stability data and ICH guidelines for this type of dosage form, including testing for pH, viscosity, particle size, resuspendability, sedimentation, antimicrobial effectiveness, and microbial burden. It also includes content testing of the three (b) (4) (methylparaben, ethylparaben, and propylparaben). The only impurity with a limit higher than the applicable ICH qualification threshold is (b) (4) with a limit of (b) (4)%, which is acceptable because this compound was confirmed in a Pharmacology Toxicology review to be an active metabolite. During stability studies, the color of the product changed from off-white to pink-orange. This change was more significant for the

higher strength. The applicant explains that the [REDACTED] (b) (4) [REDACTED] the excipient magnesium aluminum silicate, and the higher strength has a higher amount of the flavoring agent.

Container Closure: amber Type III glass bottle with a white HDPE Child Resistant Closure.

Expiration Date & Storage Conditions: 24 months at room temperature. After initial use: up to one month at room temperature.

The 40 mg/5 mL strength (batch 019236) used in the bioequivalence study is one of the primary stability batches supporting the NDA. All batches have the commercial formulation and were manufactured at the commercial site and scale, by the commercial process, and packaged in the commercial container closure system.

C. Summary of Drug Product Intended Use

| | |
|--|---|
| Proprietary Name of the Drug Product | [not finalized by GRMP goal, see the CDTL memo] |
| Non-proprietary Name of the Drug Product | simvastatin oral suspension |
| Established Name | simvastatin |
| Proposed Indication(s) | [not finalized by GRMP goal, see the CDTL memo] |
| Duration of Treatment | chronic |
| Maximum Daily Dose | 80 mg |
| Alternative Methods of Administration | n/a |

D. Biopharmaceutics Considerations

Simvastatin has the BCS designation of II (poor solubility, high permeability).

One fasting bioequivalence study was conducted to compare the 40 mg/5 mL strength of the product to the listed Zocor 80 mg relied upon (details of these studies are found in the Clinical Pharmacology review). The 40 mg/5 mL strength (batch 019236) used in the bioequivalence study is one of the primary stability batches, has the commercial formulation, and was manufactured at the commercial site and scale, by the commercial process, and packaged in the commercial container closure system.

A biowaiver request is submitted for the 20 mg/5 mL strength. The two strengths are not dose-proportional but have the same inactive ingredients with minor differences in the amounts. The two strengths have comparable in vitro dissolution profiles. Therefore, the biowaiver request of lower strength drug product (20 mg/5 mL) is granted provided that bioequivalence is established (see the Clinical Pharmacology review) between the higher strength (40 mg/5 mL) and Zocor 80 mg.

Adequate data have been provided in support of the dissolution test method, which was demonstrated to have discriminatory power to distinguish different particle size distributions. The proposed acceptance criteria are currently acceptable (see Attachment for additional information).

E. Novel Approaches: not applicable

F. Any Special Product Quality Labeling Recommendations:

- 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”.

G. Life Cycle Knowledge Information (see Attachment)

**OVERALL ASSESSMENT AND SIGNATURE:
EXECUTIVE SUMMARY**

Application Technical Lead Signature: I concur with the reviewers’ conclusions.

Suong T. Tran -
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Digitally signed by Suong T. Tran -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Suong T. Tran -S,
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Date: 2016.03.17 13:14:19 -0400

Suong (Su) Tran, PhD, Quality/CMC Lead, OPQ

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

/s/

ROBYN S JORDON
04/28/2016