CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 19-766/S030

Trade Name: Zocor Tablets

Generic Name: Simvastatin

Sponsor: Merck & Company, Inc.

Approval Date: September 24, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-766/S030

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-766/S030

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-766/S-030

SEP 24 1998

Merck & Co., Inc.
Attention: Charles Hyman, M.D.
Director Regulatory Affairs
P.O. Box 4
West Point, PA 19486

Dear Dr. Hyman:

Please refer to your supplemental new drug application dated March 24, 1998, received March 25, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zocor (Simvastatin) Tablets.

The user fee goal date for this application is September 25, 1998.

This supplemental new drug application provides for an alternate site for film-coating of 40 mg strength tablet cores at the Merck Manufacturing Division facility in Arecibo, Puerto Rico.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Margaret Simoneau, R.Ph., Regulatory Management Officer, at (301) 827-6418.

Sincerely,

Stephen K. Moore 9/24/98

Stephen K. Moore, Ph.D.
Chemistry Team Leader I for
Division of Metabolic and
Endocrine Drug Products (HFD-510)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 19-766
HFD-510/Div. Files
HFD-510/M. Simoneau
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director/SKelly
DISTRICT OFFICE

Drafted by: Mas/September 21, 1998
Initialed by:SKelly9.21.98/SMoore9.21.98/HAhn9.23.98/EGalliers9.23.98
final:Mas9.24.98
filename: 19766.30

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-766/S030

CHEMISTRY REVIEW(S)

ORIGINAL

SEP 3 1998

CHEMIST'S REVIEW

1. ORGANIZATION CDER/HFD-510 Division of Metabolism and Endocrine Drug Products	**2. NDA #** 19-766 Original NDA approved: 23-DEC-1991
3. NAME AND ADDRESS OF APPLICANT Merck & Co., Inc. P.O. Box 4 West Point PA 19486 (Phone): 610-397-2944	**4. SUPPLEMENT** SCM-030 24-MAR-98
	5. Name of the Drug ZOCOR™
	6. Nonproprietary Name Simvastatin
7. SUPPLEMENT PROVIDES for an alternate site for film-coating of 40 mg-strength tablet cores at the Merck Manufacturing Division facility in Arecibo, PR.	**8. AMENDMENT** --

9. PHARMACOLOGICAL CATEGORY HMG-CoA inhibitor used to treat hyper-lipidemia	**10. HOW DISPENSED** Oral	**11. RELATED** -N. A. -
12. DOSAGE FORM Tablet	**13. POTENCY** 40 mg	

14. CHEMICAL NAME AND STRUCTURE

Butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8α-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1α,3α,7β,8β(2S*,4S*),-8αβ]]; $C_{25}H_{38}O_5$, F.W. = 418.57, CAS 56180-94-0 (For the structure, see Chemistry Review #1, dated 16-MAR-1988 in Vol. 3.1 of NDA 19-766).

15. COMMENTS See next page.

16. CONCLUSIONS AND RECOMMENDATIONS Satisfactory CMC information has been provided for film coating of tablet core at the Arecibo, PR facility. From the Chemistry point of view, this supplement can be approved. Issue approval letter.

17. REVIEWER NAME (AND SIGNATURE) **DATE**

COMPLETED 03-SEP-1998 Sharon Kelly Sept 3, 1998

Sharon Kelly, PhD

R/D INITIATED BY

filename: 19766NDASup

DISTRIBUTION: Original: sNDA 19-766 cc: HFD-510 Division File CSO Reviewer

AP

Stephen K. Moore 9/3/98

COMMENTS (cont.)

This supplement provides for a change in the site to film-coat 40-mg tablets of Zocor at Aricebo PR rather than [redacted] The sponsor has provided adequate indication that the alternate facility will utilize the same equipment and procedures at the same scale for the process as is currently performed at the approved site in [redacted]. The sponsor has also included comparative batch results, comparative multi-point dissolution data, and comparative stability data for tablets coated at both facilities, and the data are acceptable. This supplement contains CMC information similar to that which was provided previously in Supplement 019 submitted November 20, 1996 and approved March 17, 1997, and in Supplement 022 submitted May 9, 1997 and approved July 18, 1997 to support the use of MMD, Arecibo as an alternate site for the film-coating of Tablets ZOCOR, 20 and 10 mg, respectively.

The firm indicated that the Arecibo facility was inspected by the San Juan District Office on May 7, 1997 as part of the Pre-approval Inspection for the manufacture of [redacted] and that all observations issued as a result of the inspection were successfully resolved. Data from the EES system verifies acceptable cGMP status (see attached).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-766/S030

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ORIGINAL

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 19-766
Zocor™
Simvastatin

SUBMISSION DATE: March 24, 1998

Merck & Co., Inc.

REVIEWER: Hae-Young Ahn, Ph.D.

SUBMISSION TYPE: Prior-approval supplement

AUG 24 1998

SUBMISSION:
In this submission the sponsor has requested approval for film-coating the core tablets Zocor® 40 mg at Merck Manufacturing Division (MMD) facility in Arecibo, Puerto Rico. (**Note:** MMD, Arecibo has been used as an alternate site for the film-coating of Tablets Zocor®, 20 mg and 10 mg.). Currently, core tablets are [redacted] The film-coated tablets are subsequently [redacted]

The equipment and critical operating parameters used at both film-coating sites (Arecibo and [redacted] are the same.

The dissolution profiles (averaged and individual data) for [redacted] of product film-coated at the MMD Arecibo and [redacted] were provided and similarity factors were calculated (f_2 = 88.3), indicating that the two products are similar at both sites.

Table 1. Average dissolution results for Tablets Zocor® 40 mg film-coated at MMD Arecibo and [redacted]. The dissolution specification for Tablets Zocor® 40 mg is minimum [redacted] lissolved in 30 minutes (Q= [redacted]

Time (min)	Wilson film-coated	Arecibo film-coated
15	[redacted]	[redacted]
30	[redacted]	[redacted]
45	[redacted]	[redacted]

RECOMMENDATION:
The Office of Clinical Pharmacology and Biopharmaceutics (OCPB)/Division of Pharmaceutical Evaluation II (DPE II) has reviewed NDA 19-766 submitted on 3/24/98 and finds it acceptable.

8/14/98

Hae-Young Ahn, Ph.D. DPE II/OCPB

RD/FT initialed by J. Hunt, Deputy Director 8/14/98

CC: NDA 19-766, HFD-510 (Simoneau, Moore), HFD-870 (M. Chen, Ahn), CDR (Murphy)
CODE:AP

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-766/S030

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-766/S-030

MERCK RESEARCH LABS
SUMNEYTOWN PIKE
P.O. BOX 4 BLA-20
WEST POINT, PA 19486

APR 6 1998

Attention: CHARLES L. HYMAN M.D.
DIRECTOR

Dear DR. HYMAN:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: ZOCOR

NDA Number: 19-766

Supplement Number: S-030

Date of Supplement: MARCH 24, 1998

Date of Receipt: MARCH 25, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on MAY 24, 1998 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

E. Galliers 4/6/98

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

2000 4.14

cc:
Original NDA 19-766/030
HFD-510/Div. Files
HFD-510/CSO/SIMONEAU

filename: C:\DATA\WPFILES\19766ACK

SUPPLEMENT ACKNOWLEDGEMENT

Charles L. Hyman, M.D.
Director
Regulatory Affairs

These copies are
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not desk copies.

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2850
215 652 5000

NDA NO. 19-766 REF. NO. S-030
NDA SUPPL FOR SCM

March 24, 1998

MERCK
Research Laboratories

Solomon Sobel, M.D. - Director
Division of Metabolism and Endocrine
Drug Products HFD-510, Room 14B-0
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 25 1998
HFD-510

reviewed
SKelly
Aug 14, 1998

Supplemental New Drug Application: NDA 19-766
ZOCOR™ (Simvastatin)

Dear Dr. Sobel:

Pursuant to Section 505(b) of the Food, Drug and Cosmetic Act and in accordance with 21 CFR 314.70(b), we submit, for your approval, a supplement to NDA 19-766.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in the Chemistry Section of the approved New Drug Application for ZOCOR™.

The attached prior-approval supplement provides for the alternate film-coating of Tablets ZOCOR™ 40 mg at the Merck Manufacturing Division (MMD) facility in Arecibo, Puerto Rico.

The location of the Arecibo facility is:

Merck Manufacturing Division
Division of Merck & Co., Inc.
Road #2, Kilometer 60.3
Bo. Sabana Hoyos
Arecibo, PR 00688

REVIEWS COMPLETED
APLTR Sep 24, 1998
CSO ACTION:
☑ LETTER ☐ N.A.I. ☐ MEMO
MAS 9-30-98
CSO INITIALS DATE

The mailing address of the Arecibo facility is:

Merck Sharp & Dohme, Quimica de Puerto Rico
P. O. BOX 6060
Barceloneta, PR 00617

ORIGINAL

Currently, core tablets are shipped from the [redacted] for film-coating. The film-coated tablets are [redacted] To improve availability of product, Merck & Co., Inc. requests approval for film-coating the core tablets at MMD Arecibo.

This supplement contains CMC information similar to that which was provided previously in Supplement 019 submitted November 20, 1996 and approved March 17, 1997, and in Supplement 022 submitted May 9, 1997 and approved July 18, 1997 to support the use of MMD, Arecibo as an alternate site for the film-coating of Tablets ZOCOR®, 20 mg and 10 mg, respectively.

The following chemistry documentation for the film-coating of Tablets ZOCOR® 40 mg is provided:

- An Updated Film-Coating Manufacturing Process Description of the Arecibo facility.
- Data comparison of representative batches film-coated [redacted] and Arecibo.
- Multi-point dissolution profiles for Tablets ZOCOR® 40 mg film-coated at the Arecibo and [redacted] acilities.
- Three month accelerated stability data for one lot of Tablets ZOCOR® 40 mg film-coated at the Arecibo facility (concurrent stability data for this batch will be provided in subsequent Annual Reports).
- Categorical Exclusion for Environmental Assessment

The Arecibo facility was inspected by the San Juan District Office on May 7, 1997 as part of the Pre-approval Inspection for the manufacture of [redacted] All observations issued as a result of this inspection were successfully resolved.

A complete field copy of this supplement has been submitted to the FDA Philadelphia District Office.

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a (k)(1)], we hereby certify that in connection with this application, Merck & Co., Inc. did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

We consider the filing of this Supplemental New Drug Application to be a confidential matter, and request the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct questions or need for additional information to Charles L. Hyman, M.D. (610/397-2850) or, in my absence, Robert E. Silverman, M.D., Ph.D. (610/397-2944).

Sincerely,

Charles L. Hyman, M.D.
Director
Regulatory Affairs

Attachments

Federal Express #1
Desk Copy: Philadelphia District Office, FDA
U.S. Customs House, Room 900
2nd & Chestnut Streets
Philadelphia, PA 19106-2973

q\robinson\murakami\zoc320