CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 19-766/S016

Trade Name: Zocor Tablets

Generic Name: simvastatin

Sponsor: Merck Research Laboratories

Approval Date: November 22, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-766/016

CONTENTS

Reviews / Information Included in this NDA Review.	
Approval Letter	X
Approvable Letter	
Labeling	
Medical Review(s)	
Chemistry Review(s)	X
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-766/S016

APPROVAL LETTER

NDA 19-766/S-016

NOV 22 1996

Merck Research Laboratories
Attention: Robert Silverman, M.D., Ph.D.
Director, Regulatory Affairs
Sumneytown Pike
BLA-20, P.O. Box 4
West Point, Pennsylvania 19486

Dear Dr. Silverman:

Please refer to your May 20, 1996, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zocor (simvastatin) Tablets.

The supplemental application provides for the addition of tests and specifications for the special excipients, butylated hydroxyanisole (BHA) and ascorbic acid, to the tests and specifications for the drug product.

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

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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, please contact Ms.Julie Rhee, Consumer Safety Officer at (301) 443-3510.

Sincerely yours,

Stephen K. Moore 11-22-96

Stephen Moore, Ph.D.
Chemistry Team Leader I, DNDC II
Division of Metabolic and
Endocrine Drug Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 19-766
HFD-510/Div. Files
HFD-510/CSO/J.Rhee
HFD-510/Berlin/SMoore
HFD-92
DISTRICT OFFICE
HFD-232

drafted: JRhee 11-20-96 c:wpfiles/supplement/19766s16.ap
r/d Initials:Berlin 11-20-96/SMoore 11-20-96/EGalliers 11-21-96
final: JRhee 11-21-96 11-21-96

APPROVAL (S-016)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-766/S016

CHEMISTRY REVIEW(S)

ORIGINAL

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER NOV 19 1996
	DMEDP II, HFD-510	19-766
3. NAME AND ADDRESS OF APPLICANT		4. SUPPLEMENT NUMBER, DATE
Merck Research Labs. Sumneytown Pike BLA-20 P.O. Box 4 West Point, PA 19486		SCS-016 5-20-96
5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
Zocor	Simvastatin	

8. SUPPLEMENT PROVIDES FOR

The addition of tests and specifications for the special excipients [redacted] to the tests and specifications for the drug product.

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
antihypercholestremic	RX	
12. DOSAGE FORM	13. POTENCY	
Tablets, Oral	5,10,20,40 mg	

14. CHEMICAL NAME AND STRUCTURE

See Chemistry Review #1

15. COMMENTS

The sponsor has provided updated specifications for each strength of Zocor tablets which include release specifications for butylated hydroxyanisole (BHA) and ascorbic acid (see attached copy). The sponsor noted in the cover letter that batch results from three different Merck manufacturing sites were analyzed in order to determine appropriate specification levels for these excipients. BHA content ranged from [redacted] ascorbic acid content [redacted] of label claim, respectively. Therefore, the sponsor has requested that release specifications for BHA [redacted] be set at [redacted] and [redacted] respectively. It may be noted that the drug substance, Simvastatin MF, contains [redacted] with release specifications of [redacted] of label claim.
(Continued next page)

16. CONCLUSION AND RECOMMENDATION

The additions to the drug product tests and specifications, the method descriptions, and method validation data are acceptable. Methods validation will be performed by FDA laboratories. Issue an approval letter.

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
WILLIAM K. BERLIN		11-19-96

DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE

Stephen K. Moore
11/19/96

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 19-766
3016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-766/S016

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date MAY 30 1996

NDA No. 19-766

MERCK RESEARCH LABORATORIES
Sumneytown Pike
BLA-20 P.O. Box 4
West Point, PA 19486

Attention: Robert E. Silverman, M.D., Ph.D, Director, Regulatory Affairs

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: ZOCOR(Simvastatin)

NDA Number: 19-766

Supplement Number: S-016

Date of Supplement: MAY 20, 1996

Date of Receipt: MAY 24, 1996

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on JUL 23 1996 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
Attention: Document Control Room
5600 Fishers Lane, HFD-510
Rockville, MD 20857

Sincerely yours,

Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office Drug Evaluation II
Center for Drug Evaluation and Research

FORM FDA 3217g (11/95)

PREVIOUS EDITION IS OBSOLETE

★ U.S. GPO: 1995-404-897/20718

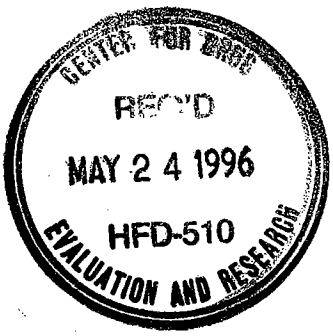
NDA SUPPLEMENT ORIGINAL

Robert E. Silverman, M.D., Ph.D.
Director
Regulatory Affairs

These copies are OFFICIAL FDA Copies
not desk copies.

Merck & Co., Inc.
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

NDA NO. 19766 REF. NO. 016
NDA SUPPL FOR SCS



MERCK
Research Laboratories

May 20, 1996

Solomon Sobel, M.D. - Director
Division of Metabolism and Endocrine
Drug Products HFD-510, Room 14B-04
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

NDA 19-766: ZOCOR™ (Simvastatin)

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

As indicated on the attached Form FDA 356h, the supplemental application provides for changes in Item 3 of the approved New Drug Application for ZOCOR™.

The attached supplemental application provides for updates of tablet specifications and HPLC methods used to determine antioxidant levels in Tablets ZOCOR™.

At this time Merck is requesting to register release specifications for butylated hydroxyanisole (BHA) and ascorbic acid [redacted] of label, respectively.

The addition of antioxidants increases the stability of Tablets ZOCOR™. Thus, simvastatin is [redacted] BHA and [redacted] ascorbic acid in the manufacture of Tablets ZOCOR™ 10, 20, and 40 mg. Tablets ZOCOR™ 5 mg and 10 mg contain the same amount of anti-oxidants resulting in [redacted] BHA and [redacted] ascorbic acid for the 5 mg strength.

Release and validation assay data of Tablets ZOCOR™ manufactured at [redacted] Merck manufacturing sites were examined to establish release specifications for BHA and [redacted] These data show BHA and ascorbic acid levels ranging from [redacted] of label, respectively. Tablets ZOCOR™ containing these antioxidant levels met all release specifications. Therefore, release specifications for BHA and ascorbic acid concentrations are set at [redacted] of label, respectively.

This supplement is organized as a series of attachments that incorporate these changes as follows:

Attachment I:	Specifications for Tablets ZOCOR™.
Attachment II:	Determination of Butylated Hydroxyanisole in Simvastatin Tablets by HPLC.
Attachment III:	HPLC Butylated Hydroxyanisole Test Method - Method Validation.
Attachment IV:	Determination of Ascorbic Acid in Simvastatin Tablets by HPLC.
Attachment V.	HPLC Ascorbic Acid Test Method - Method Validation.

The changes will become effective on or about June 17, 1996 and will apply to all packages of ZOCOR™ distributed from the company's manufacturing facilities at Wilson, North Carolina and Caguas, Puerto Rico.

Pursuant to 21 CFR 314.70(a), a complete field copy of the supplement has been submitted to the FDA Philadelphia District Office.

As required by Section 306(k)(l) of the Generic Drug Enforcement Act [21 U.S.C. 335a (k)(l)], 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 to make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this supplemental application should be directed to Robert E. Silverman, M.D., Ph.D. (610/397-2944) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

REVIEWS COMPLETED

CSO ACTION:
☑ LETTER ☐ N.A.I. ☐ MEMO

11-22-96
CSO INITIALS DATE

Sincerely yours,

Robert E. Silverman, M.D., Ph.D.
Director, Regulatory Affairs

Attachments

Certified No. P. 914 178 325

Desk Copy: Philadelphia District Office, FDA
U.S. Custom House, Room 900
2nd & Chestnut Streets
Philadelphia, PA 19106-2973

q:\saxon\murakami\19-766\spsubchg.doc