CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-766/S012

Trade Name: Zocor Tablets

Generic Name: Simvastatin

Sponsor: Meck & Co, Inc.

Approval Date: August 1, 1995

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APPLICATION NUMBER:

19-766/S012

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Reviews / Information Included in this NDA Review.

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APPLICATION NUMBER:

19-766/S012

APPROVAL LETTER

NDA 19-766/S-012

AUG - 1 1995

Merck & Co., Inc.
Attention: Robert E. Silverman, M.D., Ph.D.
Director, Regulatory Affairs
BLA-30
WEST POINT PA 19486

Dear Dr. Silverman:

Please refer to your March 17, 1995, 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 a change in the [redacted] drug product from a range of [redacted] LOD to a range [redacted] LOD prior [redacted].

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.

Sincerely yours,

7/31/95

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

cc: Original NDA
DISTRICT OFFICE
HFD-80
HFD-232
HFD-510
HFD-510/SAurecchia/WBerlin/EBarbehenn
HFD-510/STrostle/07/21/95/ft/stt/07/31/95 \N19766AP.012
ST 7/31/95
Concurrence: YChiu 07.22; WBerlin 07.24; RHedin for EGalliers 07.28.95

APPROVAL (AP: N19-766/S-012)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-766/S012

CHEMISTRY REVIEW(S)

ORIGINAL
JUL 11 1995

CHEMIST'S REVIEW	1.ORGANIZATION	2. NDA NUMBER
	DMEDP, HFD-510	19,766

3. NAME AND ADDRESS OF APPLICANT	4.SUPPLEMENT NUMBER,DATE
Merk Research Laboratories Sumneytown Pike West Point PA 19486	SCS-012 3/17/95

5. NAME OF THE DRUG	6. NONPROPRIETARY NAME	8.AMENDMENTS/REPORT,DATE
Zocor	Simvastatin	

7. SUPPLEMENT PROVIDES FOR:	
A change in the [redacted] drug product from a range of [redacted] LOD to a range of [redacted] LOD prior [redacted]	

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11.RELATED IND/NDA/DMF
Antihypercholesteremic agent	RX	

12. DOSAGE FORM	13. POTENCY
Tablets for Oral ingestion	5,10,20,40 mg

14. CHEMICAL NAME AND STRUCTURE.

see next page

15. COMMENTS

This supplement was submitted to correct discrepancies between the NDA file and actual production practice. Assay data (% Simvastatin remaining) were provided for market package stability tests for tablets produced with [redacted] LOD ranging from [redacted] (attachment 1, original NDA stability batch data, submitted 3/16/90, batch records will be provided on request). Data analysis (95% lower confidence limit) demonstrate that all market-containers used provided Drug Product stability within specifications during [redacted] Additional experiments were conducted on the final market formulation to evaluate the influence of [redacted] on drug product stability. A [redacted] of Zocor was [redacted] LOD. These samples, stored in HPDE bottles/[redacted] Finally, Stability data [redacted] each of 5, 10, 20, and 40 mg tablets Zocor (attachment II), including assay and dissolution, were provided. These batches had [redacted] ranging from [redacted] LOD, and all values of assay and dissolution were within specifications during a [redacted] period. The process controls section has been revised to reflect the change in [redacted] LOD (attachment III).

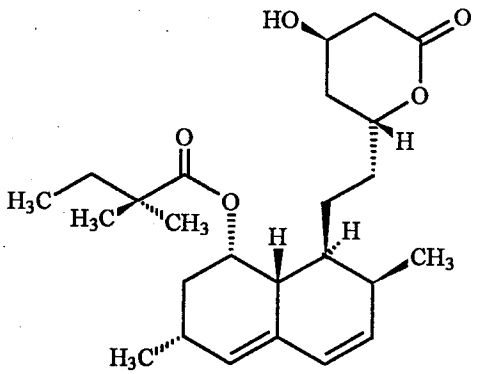
16. CONCLUSION AND RECOMMENDATION

The data support the position that [redacted] LOD, in the range of [redacted] does not impact the stability attributes of the Drug Product. The Supplement is acceptable. Issue an approval letter.

17. NAME	REVIEWER SIGNATURE	DATE COMPLETED
William K. Berlin	[signature]	7/11/95

DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE

[signature] 7/11/95



Name: Simvastatin
Proprietary: Zocor
IUPAC: [1S-[1a,3a,7b,8b,(2S*,4S*),8ab]]-1,2,3-,7,8,8ab]]-1,2,3,7,8,8a,Hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-napthalenyl 2,2-dimethylbutanoate

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APPLICATION NUMBER:

19-766/S012

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date MAR 23 1995

NDA No. 19-766

Merck & Co., Inc.
BLA-30
West Point PA 19486

Attention: Robert E. Silverman, M.D., Ph. D.

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: ZOCOR

NDA Number: 19-766

Supplement Number: S-012

Date of Supplement: March 17, 1995

Date of Receipt: March 20, 1995

Unless we find the application not acceptable for filing, the filing date will be 60 days from the receipt date above.

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Attention: Document Control Room 14B-03
5600 Fishers Lane, HFD-510
Rockville, MD 20857

Sincerely yours,

Supervisory Consumer Safety Officer
Division of Metabolism and Endocrine Drug Products
Center for Drug Evaluation and Research

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

NDA SUPPLEMENT

These copies are
OFFICIAL FDA COPIES
not desk copies.

ORIGINAL

Merck & Co., Inc.
BLA-30
West Point PA 19486
Fax 610 397 2335
Tel 610 397 2944
215 652 5000

NDA NO. 19-766 REF. NO. 012

NDA SUPP FOR SCS

MERCK
Research Laboratories

March 17, 1995

Chem Rev 07/11/95

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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 20 1995
HFD-510

Noted
EKB
7/18/95

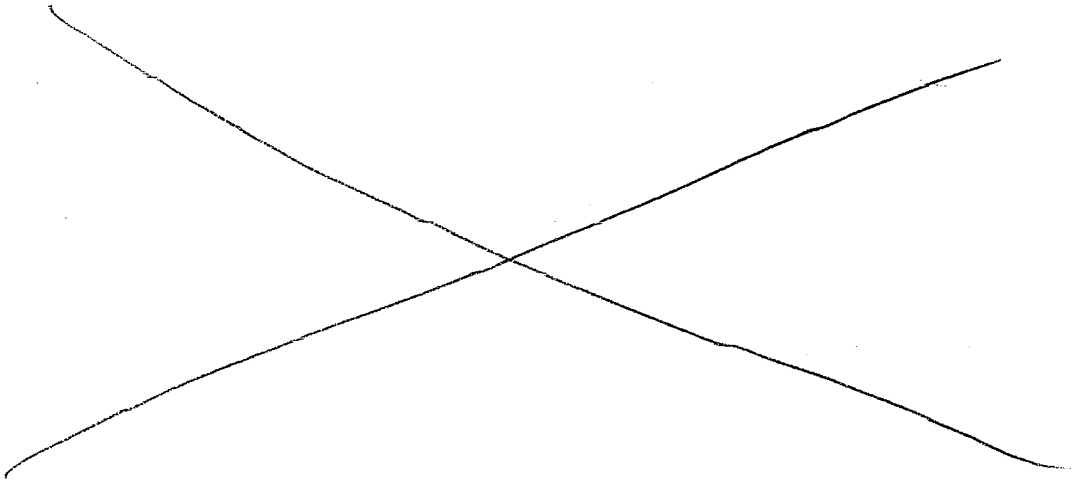
Dear Dr. Sobel:

Supplemental New Drug Application
Expedited Review Requested
NDA 19-766 Tablets ZOCOR (Simvastatin)

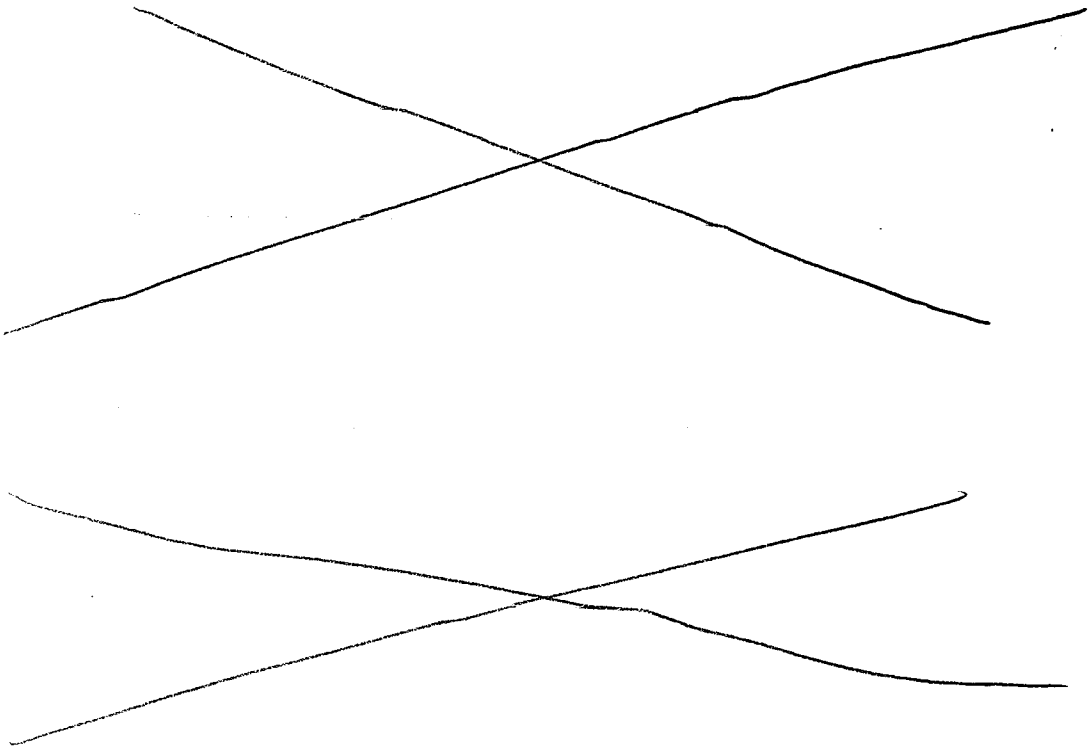
Pursuant to section 505(b) of the Food, Drug and Cosmetic Act and in accordance with 21 CFR 314.70(b), we submit, for your approval, a supplement to the approved New Drug Application for Tablets ZOCOR. This supplement provides for the expansion of an [redacted], control utilized during the manufacture of the drug product. We propose changing the [redacted] LOD at [redacted]

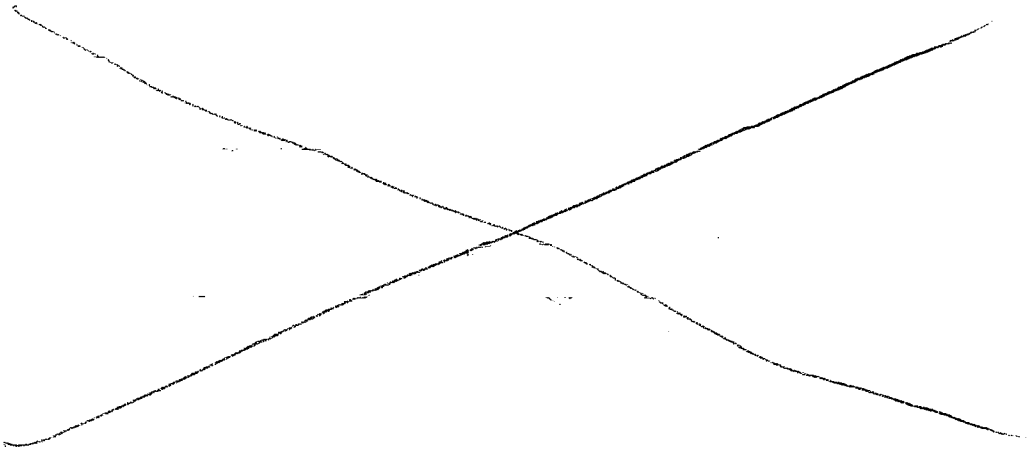
Reference is made to several telephone conversations between Dr. Silverman and Dr. Chiu or Dr. Rhee between January 17 and 27, 1995 and a letter to the Agency dated February 1, 1995, summarizing these discussions. Based on the discussions with the Division noted above, Merck is submitting the Supplemental New Drug Application in order to bring the NDA file into concordance with established and ongoing practice.

Tablets ZOCOR are manufactured by a [redacted] process. The 10 mg, 20 mg, and 40 mg strengths are [redacted] in composition. [redacted] The discussion which follows applies equally for all strengths of Tablets ZOCOR.

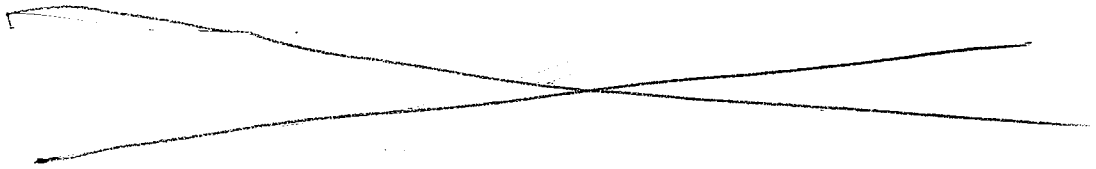


A review of the original NDA stability batches has revealed that the batch records provided upon request). The stability profile of these batches was excellent and formed the basis of the current expiration dating for Tablets ZOCOR (Attachment 1: data originally submitted on March 16, 1990 in NDA 19-766, Item 3, pages 5-6, 15-28).





production has not impacted tablet stability, as well. Attachment II contains stability data for production lots manufactured within the proposed range.



Proposed revisions to Item 3 of the NDA are provided in Attachment III (hand annotated and clean copy). All other product specifications for Tablets ZOCOR will remain as approved in the NDA.

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 subsection 306 (a) of (b) of the Act.

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

We consider the filing of this supplement to NDA 19-766 to be a confidential matter, and request that 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.

Questions concerning this supplemental application should be addressed to Robert E. Silverman, MD, Ph.D. at 610-397-2944 or in my absence, Dr. Bonnie J. Goldmann, Executive Director, at 610-397-2383.

Sincerely,

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

mcs/q/ltr/179

Attachment

Federal Express #3945719293

Desk Copy: Dr. Y.Y. Chiu, HFD-510, Rm. 14B-04, Federal Express #3945719293
Dr. M.J. Rhee, HFD-510, Rm. 14B-04, Federal Express #3945719293
FDA Philadelphia District Office
U.S. Customs House
7th & Chestnut Streets
Philadelphia, PA 19106-2973, Federal Express #3945719282