

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 19766/S029

Trade Name: ZOCOR TABLETS

Generic Name: SIMVASTATIN

Sponsor: MERCK AND COMPANY, INC

Approval Date: 06/29/98

Indication(s): DECREASING THE LDL/HDL RATIO IN PATIENTS WITH PRIMARY HYPERCHOLESTEROLEMIA.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 19766/S029

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				X
Approvable Letter				X
Final Printed Labeling		X		
Medical Review(s)				X
Chemistry Review(s)				X
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology	X			
Biopharmaceutics Review(s)				
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 19766/S029

APPROVAL LETTER

NDA 19-766/S-029

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

JUN 29 1998

Dear Dr. Hyman:

Please refer to your supplemental new drug application dated February 20, 1998, received February 23, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zocor (Simvastatin) tablets.

The supplemental application provides for changes in the CONTRAINDICATIONS, WARNINGS/ Skeletal Muscle, and PRECAUTIONS/ Drug Interactions sections of the Mevacor package insert. These include:

CONTRAINDICATIONS

“Concomitant therapy with the tetralol-class calcium channel blocker mibefradil (see WARNING, Skeletal Muscle and PRECAUTIONS, Drug Interactions)” has been added.

WARNINGS, Skeletal Muscle

“Rhabdomyolysis has occurred with simvastatin in combination with the tetralol-class calcium channel blocker mibefradil which is a potent inhibitor of cytochrome P-450 3A4 (see CONTRAINDICATIONS)” has been added.

PRECAUTIONS, Drug Interactions

Mibefradil is added as the first drug in the list of drugs for which interactions have been reported.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated February 20, 1998, with the revisions listed below. Accordingly, this supplemental application is approved effective on the date of this letter. The revision is as follows:

Delete the entire “Other Concomitant Therapy” paragraph from the “Drug Interactions” subsection of the PRECAUTIONS section of the package insert. The revision is a term of the supplemental NDA approval.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 19-766/S-029. Approval of this

submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

APPEARS THIS WAY
ON ORIGINAL

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 Margaret Simoneau, R.Ph., Regulatory Management Officer, at (301) 827-6418.

Sincerely yours,

/S/ 6/29/98

Solomon Sobel, M.D.

Director

Division of Metabolic and Endocrine Drug
Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

cc:

Original NDA 19-766

HFD-510/Div. files

HFD-510/CSO/M. Simoneau

HFD-510/D.Orloff/S.Kelly/S.Moore/R.Steigerwalt/R.Shore/H-YAhn

DISTRICT OFFICE

HF-2/Medwatch (with labeling)& labeling review

HFD-92/DDM-DIAB (with labeling)

HFD-40/DDMAC (with labeling)

HFD-613/OGD (with labeling)

HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.

HFI-20/Press Office (with labeling)

APPEARS THIS WAY
ON ORIGINAL

Drafted by: Mas/June 12, 1998/19766.29

Initialed

by:D.Orloff6.17.98/S.Kelly6.17.98/S.Moore6.18.98/R.Steigerwalt6.18.98/R.Shore6.14.98/A.

Ahn6.17.98/E.Galliers6.26.98

final: Mas 6.26.98

APPEARS THIS WAY
ON ORIGINAL

APPROVAL (AP)

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19766/S029

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

MAY 20 1998

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 19-766/SLR-029	SUBMISSION DATE:	20-FEB-98
BRAND NAME:	Zocor™ Tablets	
GENERIC NAME:	Simvastatin	
REVIEWER:	Robert M. Shore, Pharm.D.	
SPONSOR:	Merck Research Laboratories, West Point, PA	APPEARS THIS WAY ON ORIGINAL
TYPE OF SUBMISSION:	SLR: labeling	

SUBMISSION:

**APPEARS THIS WAY
ON ORIGINAL**

There have been recent reports of rhabdomyolysis with concomitant use of simvastatin (Zocor) and the calcium channel blocker mibefradil (Posicor). This submission contains revised labeling for Zocor which includes information on this clinical drug-drug interaction.

The changes include:

1. An indication that rhabdomyolysis has occurred with concomitant use of simvastatin and mibefradil,
2. A contraindication for concomitant mibefradil-simvastatin therapy,
3. Under 'Drug Interactions: Other Concomitant Therapy', mibefradil has been exempted from the general term 'calcium channel blockers'.

RECOMMENDATION:

These changes are acceptable to OCPB. However, as has already been conveyed to DMEDP, it is suggested that the whole 'Drug interactions: Other Concomitant Therapy' section be re-evaluated. If specific analysis were not done for each concomitant medication used in clinical studies, or if the usage of certain medications was sparse, there is little or no value in stating 'Although specific interaction studies were not performed, in clinical studies, Drug X was used concomitantly with Drug A, Drug B, ... without evidence of clinically significant adverse interactions.'

Robert M. Shore, Pharm.D.
 Division of Pharmaceutical Evaluation II
 Office of Clinical Pharmacology and Biopharmaceutics

/S/

20-MAY-98

RD initialed by Hae-Young Ahn, Ph.D., Team Leader

/S/

FT initialed by Hae-Young Ahn, Ph.D., Team Leader

/S/

5/26/98

CC: NDA 19-766/SLR-029 (orig.,1 copy), HFD-510(Orloff, Simoneau), HFD-870(Shore, Ahn, ChenME), CDR (Barbara Murphy).

Code: AP

**APPEARS THIS WAY
ON ORIGINAL**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19766/S029

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE



Food and Drug Administration
Rockville MD 20857

NDA 19-766/S-029

MAR - 5 1998

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

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

Dear Dr. C.L. Hyman:

APPEARS THIS WAY
ON ORIGINAL

We acknowledge receipt of your supplemental application for the following:

Name of Drug: ZOCOR (Simvastatin) Tablets

NDA Number: 19-766

Supplement Number: S-029

Date of Supplement: February 20, 1998

Date of Receipt: February 23, 1998

APPEARS THIS WAY
ON ORIGINAL

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on April 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

APPEARS THIS WAY
ON ORIGINAL

Sincerely, /S/

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

NDA 19-766/S-029
Page 2

cc:

Original NDA 19-766/S-029
HFD-510/Div. Files
HFD-510/CSO/M. Simoneau

APPEARS THIS WAY
ON ORIGINAL

filename:

SUPPLEMENT ACKNOWLEDGEMENT

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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

February 20, 1998

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

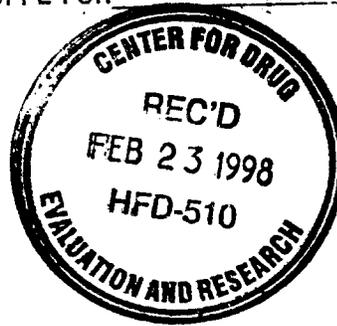
Dear Dr. Sobel:

NDA SUPPLEMENT
These copies are OFFICIAL FDA Copies
not desk copies.

NDA NO. 19766 REF. NO. 0200
NDA SUPPL FOR SUB

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

ORIGINAL



MERCK
Research Laboratories

APPEARS THIS WAY
ON ORIGINAL

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED
NDA 19-766: ZOCOR™ (Simvastatin)

*Changes noted.
They are acceptable
IS/*
3-10-98

Reference is made to the above New Drug Application, and conversations between Dr. Charles Hyman (MRL) and Dr. David Orloff (FDA) on January 12 and 13, 1998.

Pursuant to Section 505(b) of the Food Drug and Cosmetic Act and in accordance with 21 CFR 314.70 (c)(2), we submit a supplement to NDA 19-766.

APPEARS THIS WAY
ON ORIGINAL

As indicated on the attached Form FDA 356h, the supplemental application provides for changes in Item 2 of the approved New Drug Application for ZOCOR™.

The circular (#7825427) has been revised to incorporate new safety information under CONTRAINDICATIONS, WARNINGS, *Skeletal Muscle*, PRECAUTIONS, *Drug Interactions* and PRECAUTIONS, *Other Concomitant Therapy*.

APPEARS THIS WAY
ON ORIGINAL

The purpose of this Safety Revision is to include new important text that will alert the prescriber to the increased risk of rhabdomyolysis if mibefradil hydrochloride (marketed as POSICOR™ by Roche) is taken concomitantly with an HMG-CoA reductase inhibitor such as ZOCOR™. This circular includes final revisions negotiated with the FDA during January 1998.

*Reviewed
IS/*
26-11-98
IS/
17-11-98

The following are attached:

APPEARS THIS WAY
ON ORIGINAL

- (1) Copy of the Summary of Revisions
- (1) Copy of the draft Package Circular annotated for revisions
- (1) Copy of WAES reports
- (15) Mounted copies of printed Package Circular #7825427

N/C
*there were no pharmacology
issues with these label changes*
IS/
2/11/98

Solomon Sobel, M.D. - Director
NDA 19-766: ZOCOR™ (Simvastatin)
Page 2

APPEARS THIS WAY
ON ORIGINAL

This circular will be used in all products distributed from the West Point, PA facility on or before August 1, 1998.

APPEARS THIS WAY
ON ORIGINAL

As required by Section 306(k)(1) of the Generic 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.

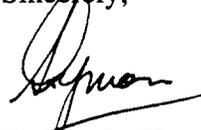
APPEARS THIS WAY
ON ORIGINAL

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.

APPEARS THIS WAY
ON ORIGINAL

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

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED	
CSO ACTION:	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
/S/	6/25/98
CSO INITIALS	DATE

Attachments

Circular #7825427

Federal Express

q\robinson\murakaim\19-766ss

APPEARS THIS WAY
ON ORIGINAL

