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

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Application Number: 19766/S029

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

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 tetratol-class calcium channel blocker mibebradil (see WARNING, Skeletal Muscle and PRECAUTIONS, Drug Interactions)" has been added.

WARNINGS, Skeletal Muscle

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

PRECAUTIONS, Drug Interactions

Mibebradil 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 form 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

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/ 6/29/99

Stephen Sobel, M.D.
Director
Division of Metabolic and Endocrine 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/M. Simoneau  
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)  

Drafted by: Mas/June 12, 1998/19766.29  
Initialed  
final: Mas 6.26.98  

APPROVAL (AP)
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:  19766/S029

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)
There have been recent reports of rhabdomyolysis with concomitant use of simvastatin (Zocor) and the calcium channel blocker mibebradil (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 mibebradil.
2. A contraindication for concomitant mibebradil-simvastatin therapy.
3. Under 'Drug Interactions: Other Concomitant Therapy', mibebradil has been exempted from the general term 'calcium channel blockers'.

These changes are acceptable to OCPB. However, as has already been conveyed to DMEPD, 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.'
APPLICATION NUMBER: 19766/S029

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE
NDA 19-766/S-029

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:

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

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

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

filename:  
SUPPLEMENT ACKNOWLEDGEMENT
Dear Dr. Sobel:

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

APPEARS THIS WAY
ON ORIGINAL

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

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 and Cosmetic Act and in accordance with 21 CFR 314.70 (c)(2), we submit a supplement to NDA 19-766.

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

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

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

The following are attached:

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

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.

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

Circular #7825427

Federal Express

qrobinson@muraaiml19-766as
Labeling Review

Application Number: NDA 19-766/S-029

Name of Drug: Zocor (Simvastatin)

Sponsor: Merck & Co.

Materials Reviewed: March 27, 1998 (S-027) last approved labeling and February 20, 1998 revised draft labeling. Review was done June 12, 1998 by Margaret Simoneau.

Background and Summary Description: February 20, 1998 (S-029) was a Change Being Effected supplement to be used on or before August 1, 1998. The changes were included in the last approved labeling dated March 27, 1998 (S-027).

It was noted that the “other Concomitant Therapy” paragraph from the “Drug Interactions” subsection of the PRECAUTIONS section of the package insert was still in the label. All manufacturers of marketed HMG-CoA reductase inhibitors have been required to delete the entire paragraph. There will be a revision as a term of the supplemental NDA approval.

Submission dated February 20, 1998 with Draft labeling has been accepted by the reviewing team members. This is Merck (#7925427).

Medical Team Leader __ ________________________ 6-17-98
Chemistry Team Leader __ ________________________ 6-18-98
Chemistry Reviewer __ ________________________ 6-18-98
Pharmacology Team Leader __ ________________________ 6-18-98
Biopharm Reviewer __ ________________________ 6-19-98
Biopharm Team Leader __ ________________________ 6-19-98
Chief, Project Manager __ ________________________ 6-26-98
Project Manager __ ________________________ 6-12-98

cc: NDA 19-744-S-029
DivFile