CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 019643/ S050

Trade Name: MEVACOR TABLETS

Generic Name: LOVASTATIN

Sponsor: MERCK and COMPANY, INC.

Approval Date: 08/12/97

Indication(s): HYPOCHOLESTEROLEMIC AGENT

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 019643/S050

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative 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 Biopharmaceutics Review(s)				X
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 019643/ S050

APPROVAL LETTER

NDA 19-643/S-050

Merck & Co., Inc.
Attention: Robert E. Silverman, M.D., Ph.D.
P.O. Box 4, BLA-20
West Point, PA 19486

AUG 12 1997

Dear Dr. Silverman:

Please refer to your supplemental new drug application dated November 27, 1996, received November 29, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mevacor™ (lovastatin) Tablets.

We acknowledge receipt of your submission dated June 27, 1997.

The supplemental application provides for revisions in the package circular for the CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, CONTRAINDICATIONS (*Pregnancy and Lactation),* PRECAUTIONS (*General, Pregnancy and Information for Patients sub-sections),* WARNINGS and ADVERSE REACTIONS (*Clinical Adverse Experiences)* sections.

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, please contact Ms. Margaret Simoneau, Consumer Safety Officer, at 301-827-6418.

Sincerely yours,

/S/ 8/11/97

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

Based on draft submitted on -
LSL -
AM

cc:
Original NDA 19-643
HFD-510/Div. Files
HFD-510/CSO/MSimoneau
HFD-510/DOrloff/WBerlin/SMoore/EBarbehenn/RSteigerwalt
HFD-820/ONDC Division Director
HFD-92/DDM-DIAB
DISTRICT OFFICE

Drafted by: JWeber/8/8/97/Merck.sap

Initialed by: WBerlin/SMoore 5/22/EBarbehenn/Rsteigerwalt 5/22/DOrloff 5/22 & 8/11/97

final: JWeber 8/11/97

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019643/ S050

MEDICAL REVIEW(S)

JAN 21 1997

NDA NO. 19-643/S-050
DRUG: MEVACOR® (lovastatin)
SPONSOR: Merck
DATE OF SUBMISSION: November 27, 1996

MEMO TO FILE

This Supplement is identical to one submitted for NDA #19-766/S-020 (simvastatin, ZOCOR®).

Please see MOR dated 1/15/97. My assessment and recommendations are the same.

/S/

Steven Aurecchia, M.D.
1/15/97

cc: NDA Arch 19-643
HFD-510
HFD-510/DOrloff/JRhee

N.B.
See my 5-15 comments on 20cor supplement and incorporate into Mevacor comments -
/S/
5-15-97

Concur
/S/
-21-97

Noted/Acceptable
3/12/97
/S/

noted
/S/
3/13/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019643/ S050

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Date DEC - 6 1996

NDA No. 19-643

MERCK RESEARCH LABORATORIES, INC.
P.O. Box 4, BLA-20
West Point, PA 19486-0004

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

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: MEVACOR (lovastatin) TABLETS

NDA Number: 19-643

Supplement Number: S-050

Date of Supplement: November 27, 1996

Date of Receipt:

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on JAN 28 1997 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,

/S/

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

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

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

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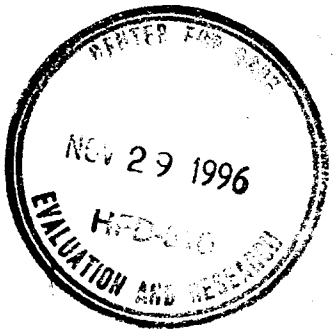
Merck & Co., Inc.
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

NDA NO. 19643 REF. NO. 050
NDA SUPPL FOR SLR

MERCK
Research Laboratories

November 27, 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:

Supplemental New Drug Application: NDA 19-643
MEVACOR™ (Lovastatin)

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 19-643.

As indicated on the attached Form FDA 356h, the supplemental application provides for changes in Item 4(c)(i) of the approved New Drug Application for MEVACOR™.

The ~~circular has~~ been revised under CLINICAL PHARMACOLOGY (pages 2-6) and ADVERSE REACTIONS, *Clinical Adverse Experiences* (pages 19, 21-22) to delete all probucol data and associated text resulting from the withdrawal of this product from the market. The INDICATIONS AND USAGE section (page 9) has been amended to include advice for the initiation of treatment based on the current NCEP Guidelines. The text under CONTRAINDICATIONS, *Pregnancy and Lactation* (page 10) and PRECAUTIONS, *Pregnancy* (page 17) has been revised to incorporate information, gathered from post-marketing surveillance, demonstrating that the incidence of adverse pregnancy outcomes in women exposed to MEVACOR™ did not exceed what would be expected in the general population. Some of the associated text has also been editorialized. Finally, the recommendation for diet, exercise and weight control under PRECAUTIONS, *General* (page 13) has been deleted because this information is already described under INDICATIONS AND USAGE and a reference to WARNINGS, Skeletal Muscle has been added under PRECAUTIONS, *Information for Patients* (Page 13).

The following are attached:

- (1) Copy of Summary of Revisions
- (1) Copy of draft Package Circular annotated for revisions
- (1) Copy of References

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.

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

REVIEWS COMPLETED
OSE DIVISION:
☐ LETTER ☐ N.A.I. ☒ MEMO
/S/ 3/11/97
OSE INITIALS DATE

Sincerely,

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

Attachments

Federal Express

APPEARS THIS WAY
ON ORIGINAL

1/15/97
see attached memo
/S/
Not Acceptable
3/12/97
/S/

NDA SUPPLAMENDMENT ORIGINAL

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

These copies are OFFICIAL FDA Copies
not desk copies.

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

June 27, 1997

MERCK
Research Laboratories

Solomon Sobel, M.D., Director
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 30 1997
HFD-510

Dear Dr. Sobel:

NDA 19-643/S-050: MEVACOR™
(Lovastatin)

Reference is made to the above Supplemental New Drug Application (submitted November 27, 1996) proposing revisions to the package circular concerning the description of current NCEP guidelines; language concerning exposure during pregnancy based on post-marketing surveillance data; and deletion of probucol data. Reference is also made to a May 23, 1997 Agency facsimile letter in which the Agency requested the insertion of two sentences after the second sentence in the new *Pregnancy* subsection paragraph.

As a result of the May 23, 1997 request, the package circular has been revised under PRECAUTIONS, Pregnancy (page 17) to amend the draft text to incorporate the Agency's request. Also included is an editorial change to the article referenced in the draft pregnancy text to replace "in-press" with the actual page numbers of the journal. All of the other changes from S-050 are include as originally submitted.

Attached are a summary of revisions and an annotated draft package circular.

If you have any questions or need additional information please contact 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
/S/ 7/11/97
CSO INITIALS DATE

Q:MURAKAMI\MEDICAL\S050AMEND

Sincerely,

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

/S/
6/30/97

Attachments
Desk Copy: Ms. Margaret Simoneau, HFD-510, Rm. 14B-04
Federal Express #1

MAY 23 1997

Regarding the following pending labeling supplements-

NDA 19-643/S-050 & NDA 19-766/S-020

DGO

The following two sentences should be inserted after the second sentence in the new *Pregnancy* subsection paragraph:

> The number of cases is adequate only to exclude a three-to-four-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified.

APPEARS THIS WAY
ON ORIGINAL

DGO

Cleared for faxing by : /S/

Solomon Sobel, MD

cc: Orig. NDAs
HFD-510/Div. Files
HFD-510/MSimoneau

APPEARS THIS WAY

ORIGINAL
AUG 19 1997

CSO REVIEW OF LABELING

NDA 19-643 SUPPL- 050 Mevacor (lovastatin) tablets
NDA 19-766 SUPPL- 020 Zocor (simvastatin) tablets
Date of this review: 23-May-1997
Draft SUBMISSION DATE: November 27, 1996
AMENDMENTS: None to date
SUPPLEMENT APPROVAL DATE: Status = PENDING

LABELING, etc. PIECES REVIEWED: MOR dated (final) 1/21/97;
PCL reviwer comments dated 3/18/97; Medical Team Leader comments undated & 5/23/97
Circular labeling presentation from Merck dated 11/27/96

REVIEW & COMMENTS:

INDICATIONS AND USAGE:

The following two footnotes were added for consistency with current NCEP guidelines.

> In CHD patients with LDL-C levels 100-129 mg/dL, the physician should exercise clinical judgment in deciding whether to initiate drug treatment.
>
> At the time of hospitalization for an acute coroary event, cosideration can be given to initiating drug therapy at discharge if the LDL-C is ≥130 mg/dL (see NCEP Guidelines, above).

CONTRAINDICATIONS:

> The following statement was deleted to conform with simultaneous changes to the PRECAUTIONS/*Pregnancy* section.
>
> > . . . . may cause fetal harm when administered to a pregnant woman. Therefore, simvastatin . . . .
>
> "Zocor" is substituted for "simvastatin" in two places.
>
> The word "immediately" is inserted in the instruction to discontinue Zocor if the patient becomes pregnant while taking the drug. And the labeling adds the instruction to "(see PRECAUTIONS, Pregnancy)."

PRECAUTIONS:

> The following sentence was deleted to the *General* subsection:
>
> > Before instituting therapy with ZOCOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other dunerlying medical problems (se INDICATIONS AND USAGE).

CC: Orig NDA 19-643-050
Orig NDA 19-766-20
Div File

To the fourth paragraph in the *General* subsection, the phrase (underlined below) was added to the sentence, "Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness particularly if accompanied by malaise or fever (see WARNINGS, Skeletal Muscle)."

PRECAUTIONS/*Pregnancy*:

Four sentences were deleted from the first paragraph following "See CONTRAINDICATIONS."

The following paragraph was added to reflect a published article that evaluated postmarketing drug exposure during pregnancy.

> Rare reports of congenital anomalies have been received following intratuerinte exposure to HMG-CoA reductase inhibitors. In a review of approximately 100 prospectively followed pregnancies in women exposed to ZOCOR or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. As safety in pregnant women has not been established and there is no apparent benefit to therapy with ZOCOR during pregnancy (see CONTRAINDICATIONS), treatment should be immediately discontinued as soon as pregnancy is recognized. ZOCOR should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

ADVERSE REACTIONS:

Probucol data were removed from the table in the *Clinical Adverse Experiences* subsection.

RECOMMENDATIONS:

Instead of issuing an approvable (AE) letter asking the firm to provide additional qualifying language to the new paragraph in the *Pregnancy* subsection, Dr. Orloff provided the exact text to be requested. Therefore, the changes will be faxed to the firm for prompt reply so an AP letter can be issued.

The following two sentences should be inserted after the second sentence in the new *Pregnancy* subsection paragraph:

> The number of cases is adequate only to exclude a three-to-four-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified.

Also, the medical reviewer recommended that the article referenced above be cited in the labeling.

Finally, the M.O. recommended that the *Pregnancy* statements be incorporated in the labeling for all HMG-Co reductase products and that the Probucol adverse reaction data be deleted from the labeling for all marketed lipid lowering drugs.

/S/

CSO signature/date 5-23-97

/S/ 5-23-97

Group Leader signature/date

APPEARS THIS WAY ON ORIGINAL

cc: Arch. NDA
HFD-510
HFD-510/CSO Simoneau
HFD-510/EBarbehenn

/S/

Pcl rev. signature/date
E. Barbehenn
8/18/97

/S/ 5/23/97

Sup.Pcl.signature/date

\19766s20.cso