PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 19-643 Supplement # 55 Circle one: (SE1) SE2 SE3 SE4 SE5 SE6

HFD 510 Trade and generic names/dosage form: MEVACOR Tablets Action: (AP) AE NA

Applicant MERCK Therapeutic Class Lipid Altering Agents

Indication(s) previously approved Reduction of elevated total + LDL (Types 2A + 2B); To slow prog of coronary atherosclerosis

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Proposed indication in this application IN THE Primary Prevention of CHD in pts with Average to mod. elevated Total-C and LDL-C, below average HDL-C, and who are at high risk for CHD based on elevated total C/HDL-C.

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ✓ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

___Neonates (Birth-1month) ___Infants (1month-2yrs) ___Children (2-12yrs) ___Adolecents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

✓ ___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing,

✓ (2) Protocols were submitted and approved.

✓ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes ✓ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from MEDICAL TEAM LEADER (e.g., medical review, medical officer, team leader)

/S/ [redacted] Med. Team Leader March 1, 1999

Signature of Preparer and Title Date

Orig NDA/BLA # 19-643
HFD-510/Div File
NDA/BLA Action Package
HFD-006/ KRoberts

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

(revised 10/20/97)

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

NDA NO. 19643 REF. NO. 055
NDA SUPPL FOR SE8

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April 28, 1998

ORIGINAL

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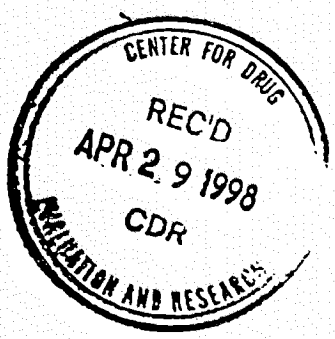

Dear Dr. Sobel:

Supplemental New Drug Application
NDA 19-643: Tablets MEVACOR™ (Lovastatin)
User Fee No. 3454

Pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act and in accordance with Title 21 of the Code of Federal Regulations, Merck Research Laboratories (MRL) is submitting a Supplemental New Drug Application (SNDA) for MEVACOR™ (Lovastatin).

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in Labeling, Clinical Documentation, Statistical Documentation, Case Report Tabulations (CRT), Case Report Forms (CRF), Patent Information and Patent Certification of the approved New Drug Application (NDA) for Tablets MEVACOR™.

MEVACOR™, also referred to as lovastatin and MK-0803, is a an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and is currently indicated as an adjunct to diet for the reduction of elevated total and LDL cholesterol levels in patients with primary hypercholesterolemia. NDA 19-643 for Tablets MEVACOR™, 20 mg was approved on August 13, 1987 (submitted on November 14, 1986). Subsequently, the labeling for MEVACOR™ was approved for the 40 mg tablet on February 21, 1991 (S-009 submitted on February 9, 1989) and for the 10 mg tablet on March 28, 1991 (S-018 submitted on July 27, 1990).

This application is based on the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS, Protocol No. 042 submitted to IND [redacted] on April 3, 1990/Serial No. 136), and supports a new indication for the primary prevention of coronary heart disease in men and women without symptomatic cardiovascular disease and with average to mildly abnormal lipid levels.

This application also includes a revised recommendation to monitor liver function tests based on safety data from the Expanded Clinical Evaluation of Lovastatin (EXCEL) study (SNDA/S-017,

submitted on June 29, 1990 and approved on December 19, 1991), AFCAPS/TexCAPS study, and spontaneous reports of liver failure or hepatitis in association with the use of lovastatin.

The results of AFCAPS/TexCAPS demonstrate that treatment with MEVACOR™ reduces the risk of developing clinically manifest coronary artery disease (myocardial infarction, unstable angina and sudden death) in healthy persons with average or mildly abnormal lipid parameters and, one or more risk factors for coronary artery disease in addition to age. These results were robust: they were consistent across endpoints, they were independent of baseline LDL-C, and the magnitude of risk reduction for subgroups, including women and the elderly, was consistent with the overall benefit.

The NHANES III survey data indicate that there are approximately 8 million Americans without documented atherosclerotic cardiovascular disease and who meet the age and lipid criteria of AFCAPS/TexCAPS. As with the AFCAPS/TexCAPS cohort, only 17% of this reference population would qualify for drug treatment by current NCEP-ATPII guidelines. Hence, over 6.5 million Americans currently not recommended for drug treatment could benefit from LDL-C reduction with MEVACOR™. Merck believes that AFCAPS/TexCAPS provides evidence that therapy with MEVACOR™ represents a safe and significant improvement in the primary prevention of atherosclerotic coronary artery disease for a sizable subpopulation of Americans for whom recommendations have heretofore been confined to diet and lifestyle modifications. The results of this study have important implications for public health and represent significant new information for prescribers and patients. Therefore, to expedite the inclusion of these results in the product labeling for MEVACOR™, Merck requests that this supplemental NDA be accorded a Priority Review Status.

MRL would like to bring to the Agency's attention the following points with regard to the submission of AFCAPS/TexCAPS. In light of the large size and duration of the study and the established safety profile of MEVACOR™, the Agency granted MRL a waiver from reporting non-serious, non-drug related adverse experiences (AEs) for AFCAPS/TexCAPS (MRL letter requesting waiver submitted on October 23, 1996, and the FDA response letter dated January 9, 1997). Therefore, this application contains all clinical events that constitute protocol defined endpoints, serious AEs, non-serious drug related AEs and AEs resulting in discontinuation (serious and non-serious).

Merck is also requesting a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.31(b). The description of the proposed action is included in volume one of this submission.

(continued)