Mr. David M. Moss
Director, Technology Support Services Staff
NDA 19-643: Tablets MEVACOR™
Supplemental New Drug Application
Lovastatin - AFCAPS/TexCAPS

cc (cover letter only):

G. Brolund, Division of Applications Development Services, HFD-72
Federal Express #2
M. Buster, Division of Infrastructure Management Services, HFD-72
Federal Express #2
K. Edmunds, Division of Technology Support Services Staff, HFD-70
Federal Express #3
D. Orloff, M.D.
HFD-510, Room 14B-04, Federal Express #4
M. Simoneau
HFD-510, Room 14B-04, Federal Express #4
W. Berlin
HFD-510, Room 14B-31, Federal Express #4
R. Steigerwalt
HFD-510, Room 14B-04, Federal Express #4
J. Mele
HFD-715, Room 14B-45, Federal Express #5

cc (cover letter with attachments):

NDA 19-643, HFD-510 (2 copies), Federal Express #4

q\robinson\murakami\mevdisk

APPEARS THIS WAY ON ORIGINAL

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

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

April 16, 1998

DESK COPY

MERCK
Research Laboratories

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products
HFD-510, Room 14B-04
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

NDA 19-643: MEVACOR™
General Correspondence

Dear Dr. Sobel:

Reference is made to the above new drug application (NDA). Reference is also made to the recently completed Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), and the attached papers and manuscripts describing the rationale, the cohort and the results of this study. Merck Research Laboratories (MRL) intends to file the results of this study as a supplemental new drug application (SNDA) for the purpose of seeking the new indication for MEVACOR™ for primary prevention of Coronary Artery Disease (CAD). Reference is further made to a telephone conversation between Dr. Charles Hyman of MRL, and Dr. David Orloff of the Food and Drug Administration (Agency), on February 28, 1998, during which the review status of this application was discussed and Dr. Orloff requested from MRL a written request and justification for a priority review of this SNDA. By this letter, MRL is notifying the Agency of its intent to file the results of AFCAPS/TexCAPS as an SNDA at the end of April, 1998.

AFCAPS/TexCAPS is a unique primary prevention cholesterol lowering study by virtue of the population studied and the implications of the results. Firstly, at baseline, the cohort for this study was free of any symptomatic and/or clinical evidence of atherosclerotic cardiovascular disease. Secondly, the cohort was selected on the basis of average or normal total and LDL- cholesterol values, with moderately reduced HDL-cholesterol. Thirdly, the study included women and elderly persons (>65 yrs), two groups generally excluded from large prior studies. When viewed from the perspective of the NCEP-ATPII guidelines, only 68% of the AFCAPS study cohort would have met current criteria for the recommendation of a fasting lipid profile, and only 17% would have been recommended pharmacologic intervention to lower cholesterol (LDL-C $\geq$160 + $\geq$ 2 RF).

The results of AFCAPS/TexCAPS demonstrate that treatment with MEVACOR reduces the risk of developing clinically manifest CAD (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 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.

We consider the information in this correspondence to be a confidential matter and request that the Food and Drug Administration not make its content nor any future communications with regard to it, public, without first obtaining the written permission of Merck & Co., Inc..

Please direct all questions or requests 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 yours,

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

Attachments

Federal Express #1

Desk Copy: Federal Express #1 David G. Orloff, M.D., with attachments, HFD-510, Rm. 14B-04
Federal Express #1 Ms. Margaret Simoneau, without attachments, HDF-510, Rm. 14B-04

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RECORD OF TELEPHONE CONVERSATION OR MEETING	DATE: Wednesday, August 19, 1998
Called Dr. Charles Hyman to request a subgroup analysis with respect to total cholesterol and HDL-C ratios. Dr. Hyman inquired as to why I am making this request and I informed him that I was curious if there was a subgroup of patients in the AFCAPS/TexCaps trial who would clearly benefit from treatment with lovastatin and if this subgroup would be those patients with TC/HDL-C > 5.0. Dr. Hyman agreed to forward the request to their biostatisticians and told me that I would likely receive a response in 1 week. /S/ [redacted]	**NDA:** 19-643/AFCAPS trial **Telecon/Meeting initiated by:** sponsor FDA • **Product name:** lovastatin **Firm name:** Merck Research Labs **Name and title of person with whom conversation was held:** Dr. Charles Hyman/Director of Regulatory Affairs **Telephone:** 610-397-2850

[redacted]

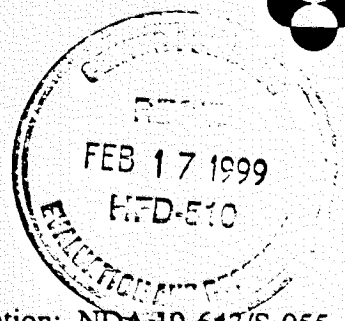
Charles L. Hyman, M.D.
Director
Regulatory Affairs

February 17, 1999

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

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products
HFD-510, Rm. 14B04
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

MERCK
Research Laboratories



Dear Dr. Sobel:

Supplemental New Drug Application: NDA 19-643/S-055
MEVACOR™ (Lovastatin)

Reference is made to the Supplemental New Drug Application 19-643/S-055 (AFCAPS/TexCAPS) for MEVACOR™ (Lovastatin) submitted on April 28, 1998. Reference is also made to the January 29, 1999 teleconference between the Food and Drug Administration (FDA) and Merck Research Laboratories (MRL) during which the labeling for AFCAPS/TexCAPS was discussed, and the revised label subsequently submitted to the Agency on February 2, 1999. Reference is further made to the February 11, 1999 facsimile from the FDA requesting MRL make additional changes to the label as listed below. By this letter, MRL is providing revised labeling that incorporates the requested changes.

Specifically, the requested changes to the text on Page 9, Clinical Studies section, second sentence have been incorporated. The cumulative incidence rates for the primary endpoint have been changed to crude rates, and the footnote on Page 10 has been deleted. As requested, we have also provided a Kaplan-Meier plot of event-free survival for Figure 1. An explanation of our analytic approach for calculating this plot is provided below. Finally, we have reintroduced the original paragraph describing the adverse events experience of the AFCAPS population. This paragraph appears on page 25 and is identical to that appearing in the original labeling submitted on April 28, 1998.

In regard to the requested Kaplan-Meier survival plot for the primary endpoint: the analysis of treatment group differences takes into account all patients and all events that occurred during the entire study. There is, however, a potential problem with the Kaplan-Meier estimator of survival rates in that it can be unduly influenced by events that occur when few patients are at risk as occurs at the end of follow-up. This is the reason for the statement in the AFCAPS/TexCAPS Data Analysis Plan Section II.A.1 (submitted on May 9, 1997, submission serial # 298): "Because Kaplan-Meier and life-table estimates can be misleading when the number of patients at risk becomes small, as it does at the end of the study, timepoints after which there are less than 500 patients left at risk in either treatment group will be combined for analysis."

One alternative considered to avoid such misleading estimates in a Kaplan-Meier curve is to provide estimates up to the timepoint, in this case ~73 months, when there were still 500 patients at risk in both treatment groups. Although valid, this approach would in effect remove late-occurring events and is in fact similar in spirit to the life-table plot previously provided.

The solution we have chosen is to include the later events in the calculation of the estimates by assuming these events occurred at the latest timepoint when there were still 500 patients at risk in both treatment groups, i.e, ~73 months. This approach has no effect on the comparison of treatment group differences but gives more realistic estimates of survival rates than a method that makes no provision for the undue influence of late-occurring events.

The problem of undue influence of late events can best be seen in an extreme example. If the participant with the longest duration of observation in the trial had an event at the end of the study when this person was the last one at risk, the final estimate of survival in that treatment group would be zero at the end of the study, no matter what the previous estimate of survival had been on the day before the event occurred. The crude survival rate could have been 99% but the Kaplan-Meier estimate at the end of follow-up would have been 0% in this case. This extreme example was the motivation behind our pre-specified rule for combining later time points.

It should be noted that life-table and Kaplan-Meier estimates of survival rates have no effect on relative risk and no effect on the comparison of treatment group differences.

We consider the information included in this submission 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.

If I can be of further assistance please do not hesitate to contact Charles L. Hyman, M.D. (610/397-2850) or, in my absence, Robert E. Silverman, M.D., Ph.D. (610/397-2944).

Sincerely,

Marie A Day for Charles L Hyman, MD

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

Attachments
Hand-delivered
Desk Copies: Hand-delivered to: Dr. Joy Mele, HFD-715, Rm. 14B45
Hand-delivered to: Dr. David Orloff, HFD-510, Rm. 14B04
Hand-delivered to: Dr. Mary Parks, HFD-510, Rm. 14B04
Hand-delivered to: Ms. Margaret Simoneau, HFD-510, Rm. 14B04