an increase of their dose to 40 mg daily in order to achieve the treatment goal of LDL-C < 110 mg/dL.

The mean percentage changes in LDL-C, TC, TG, and HDL-C in AFCAPS/TexCAPS are not different from previously conducted trials whose results are already reflected in the label and hence reporting these results would be repetitious. The reporting of endpoint results should be as crude incidence rates or should specify the number of observed events in each treatment group and should distinguish between primary versus secondary endpoints as follows:

DRAFT LABELING

[redacted]

Discussion of subgroup analyses should include only data which were conclusive with emphasis placed on the subgroup with ≥ 2 risk factors as it was clearly this population to whom the benefits of treatment applied.

DRAFT LABELING

[redacted]

The primary endpoint results should be depicted graphically as a Kaplan-Meier plot of event free survival.

Indications and Usage

The introductory paragraph should delete "and/or" in describing individuals for whom MEVACOR is indicated as follows:

DRAFT LABELING

[redacted]

The subheading, *Primary Prevention of Coronary Heart Disease*, should accurately and succinctly describe the AFCAPS/TexCAPS cohort and results as follows:

DRAFT LABELING

[redacted]

DRAFT LABELING

Acute major coronary events was deleted because MI and unstable angina, not fatal events, were the coronary events which had significant risk reductions with lovastatin therapy. Reference to the Clinical Pharmacology, Clinical Studies section is made here to better describe the AFCAPS/TexCAPS cohort and results without being redundant.

Warnings

The current proposed label revision removes the recommendation for performing liver function tests at 6 and 12 weeks after therapy initiation or dose elevation and states periodic monitoring is not necessary after 1 year of stable dose therapy. The safety review of AFCAPS/TexCAPS revealed clinically important elevations in hepatic transaminases as early as 12 weeks and as late as 5.2 years. Although the incidence of these elevations is rare (0.6%) there is **no evidence** that these abnormalities occur **only within** the first year after initiation of therapy or dose elevation. Because treatment of hypercholesterolemia is a chronic therapy in a population likely to be started on other medications (the AFCAPS/TexCAPS cohort demonstrated an increase in concomitant medication use from baseline) with potential for drug-drug interactions, there should be a recommendation to clinicians who prescribe lovastatin to periodically monitor their patients even after the first year of therapy.

Dosage and Administration

Reference to NCEP guidelines should not be deleted as a recommended goal of therapy and the following revision should be inserted to include AFCAPS/TexCAPS findings in the treatment of individuals for primary prevention of coronary heart disease:

DRAFT LABELING

RECOMMENDATIONS

Contingent upon changes to the proposed labeling as outlined above, this supplemental NDA should be approved.

/S/ 2/24/99
Mary Parks, M.D.
Medical Officer

/S/
Joy D. Mele, M.S.
Mathematical Statistician

Concur:
Ed Nevius, Ph.D. /S/ 2/24/99
Director of DOB2

/S/
Todd Sahlroot, Ph.D.
Biometrics Team Leader

David G. Orloff, MD
Medical Team Leader /S/ 2/24/99

Recommendation code: ~~AE~~
AP 2/25/99

/S/

/S/ 3/9/99

Memorandum
To: David Orloff, MD; Joy Mele, MS; Margaret Simoneau, RPh; Jayne Peterson, JD
From: Mary Parks, MD
Date: January 27, 1999
Subject: Teleconference with Merck on Friday, 1/29 at 10am

The following revisions were faxed to Charles Hyman, MD at Merck on Monday, January 25th, and will be the topics of discussion during the teleconference. In addition, Joy and I have looked at the liver function test results in AFCAPS/TexCAPS and this issue should be raised during the teleconference. I have included a table from my review on this issue which was not included in the materials sent to Merck.

- ***Page 2, Clinical Pharmacology section, 1st paragraph, 2nd sentence revised. Delete second paragraph describing AFCAPS/TexCAPS.***

DRAFT LABELING

[redacted]

- ***Page 8, Clinical Studies section, 1st and 2nd paragraph revised.***

DRAFT LABELING

[redacted]

- ***Page 9, Clinical Studies section, 1st sentence deleted and rest of paragraph revised.***