- ***Page 10, Clinical Studies section, Figure 1 to use survival curve to describe primary endpoint results.***

- ***Page 12, Indications and Usage section, 1st paragraph, 1st sentence revised. Subheading for Primary Prevention of Coronary Heart Disease revised.***

- ***Page 28, Dosage and Administration section, 2nd paragraph, 3rd sentence revised.***

- ***Please note: Revisions for Warnings section regarding liver function tests monitoring are pending.***

Abnormalities of Liver Function Tests

Clinically important elevations of LFTs were classified as **consecutive elevations of hepatic transaminases (AST or ALT) > 3 times ULN** (AST 111 IU/L and ALT 120 IU/L). The incidence of consecutive elevations of AST and/or ALT > 3 times ULN was not significantly different between the 2 treatment groups (18 (0.6%) lovastatin vs. 11 (0.3%) placebo). When evaluated for time to event, of the 18 lovastatin-treated subjects who developed clinically relevant elevations of LFTs, 9 occurred within the first year of therapy and 9 occurred after 1 year of therapy. None of these cases occurred within the first 12 weeks of therapy. Eleven of these cases were possibly drug-related with most enzyme elevations resolving with interruption of therapy. The other patients had coexistent conditions (e.g. gallstones, pancreatitis, viral hepatitis) which may have contributed to the enzyme elevations. Table 19 summarizes the results of the patients with clinically important elevations of LFTs.

Table 19. Lovastatin treated subjects with consecutive elevations of AST and/or ALT > 3 times ULN

Patient ID	Days Into Study	Dose	Range of LFT Abnormality	Action Taken	Possibly Related to Lovastatin
Within 1st year of study					
5808	90	20 mg	ALT 257-620 IU/L	drug interrupted	Y
5247	127	20 mg	ALT 138-149 IU/L	none	Y
9352	127	20 mg	ALT 122-508 IU/L	drug discontinued	N
0067	171	40 mg	ALT 122-166 IU/L	drug discontinued	N
1203	226	20 mg	ALT 143-1390 IU/L	drug discontinued	N
0603	247	20 mg	ALT 147-232 IU/L	drug interrupted	Y
6793	269	40 mg	ALT 153-592 IU/L	drug interrupted	Y
0174	335	40 mg	AST 152-375 IU/L	none	Y
0003	338	40 mg	ALT 147-218 IU/L	drug interrupted	Y
After 1 year of therapy					
0136	421	20 mg	ALT 139-161 IU/L	none	N
1242	567	20 mg	ALT 236-438 IU/L	drug interrupted	N
9546	599	20 mg	ALT 124-264 IU/L	drug interrupted	Y
3023	900	20 mg	ALT 138-164 IU/L	drug interrupted	Y
0177	910	20 mg	ALT 147-374 IU/L	drug interrupted	Y
1584	1055	40 mg	ALT 126-157 IU/L	none	N
5327	1191	40 mg	ALT 162-181 IU/L	drug interrupted	Y
2001	1742	20 mg	ALT 243-525 IU/L	none	N
0296	1954	20 mg	ALT 202-518 IU/L	drug interrupted	Y

Reviewing these cases on an individual basis the following conclusions were made:

- Clinically important elevations of LFTs were identified within and after the 1st year of treatment with lovastatin with 50% of the cases identified in this clinical trial occurring after 1 year.
- The majority of cases resolved with study drug discontinuation or interruption.
- There were no severe adverse events reported as a consequence of these liver test abnormalities. However, either an interruption or discontinuation of therapy was instituted in the majority of these cases and the consequence of continued therapy in the setting of a clinically important LFT elevation is unknown from this trial.

Joy also examined the relationship between baseline and initial 3 month LFT elevations and elevations after more than 100 days of therapy and found that neither baseline measurements nor measurements during the first 3 months are predictive of later LFT elevations.

SPONSOR'S PROPOSED LABELING

Lovastatin is currently indicated as an adjunct to diet for the reduction of elevated total and LDL-C levels in patients with primary hypercholesterolemia (Types IIa and IIb), when the response to diet restricted in saturated fat and cholesterol and to other nonpharmacological measures alone has been inadequate. Based on data from the AFCAPS/TexCAPS the major proposed changes to the labeling includes:

Clinical Pharmacology

- The LRC-CPPT data are deleted and replaced with a introductory statement and description of the AFCAPS/TexCAPS trial. The description is restated in the *clinical studies* section. The patient population described in this section included men and women without symptomatic cardiovascular disease with average to mildly elevated TC and LDL-C levels and below average HDL-C levels compared with the National Health and Nutrition Education Survey (NHANES) III data.

Indications and Usage

- A revised introductory statement and a subheading on Primary Prevention of Coronary Heart Disease is added stating the use of mevacor is indicated to reduce the risk of acute major coronary events, myocardial infarctions, unstable angina, and coronary revascularization procedures.
- Separate subheadings for Coronary Heart Disease and Hypercholesterolemia are included.

Warnings

- Proposed changes to this include a statement regarding no significant differences between lovastatin 20 mg and 40 mg qd from placebo with respect to consecutive elevations of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) based on the AFCAPS/TexCAPS data. Data from the Expanded Clinical Evaluation of Lovastatin (EXCEL) study also support the relative safety of lovastain 40 mg or less daily and the sponsor recommends liver function tests (LFTs) be performed before treatment initiation and periodically thereafter (e.g. seminannually) in lieu of the previous recommendation of 6 and 12 weeks after treatment initiation. For patients titrated to 80 mg daily it was recommended to repeat an additional set of LFTs at 3 months.

Dosage and Administration

- The deletion of a reference to the NCEP guidelines as a recommended goal of lovastatin therapy was made based on the results of AFCAPS/TexCAPS.

REVIEWER'S COMMENTS ON LABELING

AFCAPS/TexCAPS studied the use of lovastatin 20 to 40 mg daily in a population of patients without symptomatic evidence of CHD and mean TC 221±21mg/dL, LDL-C 150 ±17 mg/dL, HDL-C 36±5 mg/dL for men and 40±5 mg/dL for women. All the patients had at least one risk factor for CHD based on age as an inclusion criterion and approximately two-thirds of the cohort had ≥ 2 risk factors of either HTN, low HDL-C, smoking, diabetes mellitus, or family history for CHD. Although comparisons were made to an age and gender matched reference population derived from the National Health and Nutrition Evaluation Survey (NHANES III) the AFCAPS/TexCAPS cohort was not representative of the U.S. general population. Furthermore, CHD incidence rates in the NHANES population were not known and extension of the benefits of lovastatin