who developed clinically relevant elevations of LFTs, 9 occurred within the first year of therapy and 9 occurred after 1 year of therapy with some reported after 5 years 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 22 summarizes the results of the patients with clinically important elevations of LFTs.

Table 22. 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

*Relationship to drug made on the basis of reviewer's judgment from review of case report tabulations and case report forms where coexistent conditions were described.

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 lovastatin treatment 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.

Liver Function Testing

The sponsor examined the relationship between early (at baseline or in the first 100 days of the study) elevations in ALT and/or AST (1 or more times the ULN) and elevations (2 or more times the ULN) occurring after more than 100 days on therapy. The sponsor concluded that "early LFT results were predictive of later LFT elevations." The sponsor also contends that measurements during the first 100 days of therapy are not more predictive of later rises than the baseline measurements. These results were submitted as rationale for modifying the labeling to exclude LFT's 6 and 12 weeks after intitiation of therapy.

This reviewer found that early measurements were not good predictors of later elevations in ALT or AST, regardless of when the measurements were taken. The table below shows the false positive (F+) and false negative (F-) error rates for lovastatin and placebo using either baseline (base) or measurements in the first 100 days (d100) as a predictor of later elevations for range of incidence rates (2% to 6%; incidence of any single LFT elevation of >2 X ULN).

	Lovastatin				Placebo			
Rate	F+/base	F+/d100	F-/base	F-/d100	F+/base	F+/d100	F-/base	F-/d100
2%	.94	.94	.02	.01	.95	.94	.02	.02
3%	.91	.91	.02	.02	.91	.91	.02	.02
4%	.88	.88	.03	.03	.89	.89	.03	.03
5%	.86	.85	.04	.03	.88	.86	.04	.04
6%	.83	.82	.05	.04	.85	.85	.05	.05

Focusing first on the false positive error rates, it is clear that these rates are consistently high indicating for a large percentage of patients (more than about 82%), a high value during initial treatment most likely does not imply a high value after prolonged treatment. The false negative rates indicate that as many as 5% of the patients who show no LFT elevation during the first 100 days of therapy may show an elevation after prolonged treatment. We can also compute predictive rates for early measurements and again we see that measurements at baseline or during the first 100 days are not predictive of later elevations with rates ranging from 11% to 14% in both treatment groups.

This reviewer would conclude that neither baseline measurements nor measurements during the first 3 months are predictive of later LFT elevations.

The latter analysis suggests that monitoring should not be restricted to early exposure. The table below further examines this issue by showing the timing of the elevations observed in this trial by treatment group and magnitude of the elevation. It is clear that a large number of first-time elevations occur after 1 year on study.

	2xULN<LFT<3xULN		LFT>3xULN	
	Lovastatin	Placebo	Lovastatin	Placebo
<=3 months	22	17	7	0
3-6 months	0	1	4	4
6-12 months	0	2	20	5
>12 months	81	87	33	29

Conclusions on Safety Results

There are no new adverse events reported in AFCAPS/TexCAPS that are not already reflected in the current label. Although the incidence of clinically important elevations of hepatic transaminases is low (<1%) these abnormalities were seen as early as 3 months and as late as 5.2 years.

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

DRAFT LABELING

[redacted]

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 lovastatin 40 mg or less daily and the sponsor recommends liver function tests (LFTs) be performed before treatment initiation and periodically thereafter (e.g. semiannually) in lieu of the previous recommendation of 6 and 12 weeks after treatment initiation. In addition, LFT monitoring would only be recommended within the first year of treatment or until one year after the last elevation in dose. 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 middle-aged men (age 45-73) and postmenopausal women (age 55-73) 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 treatment from AFCAPS/TexCAPS could not be made to this reference population. Indeed, AFCAPS/TexCAPS targeted an at-risk population for developing CHD with participants having a lower HDL-C (22nd percentile compared to NHANES), higher TC/HDL-C and LDL-C/HDL-C ratios, and higher LDL-C (60th percentile). Although AFCAPS/TexCAPS demonstrated a 37% risk reduction ($p<0.001$) in combined primary endpoints in lovastatin group with similar trends in five of the secondary endpoints, subgroup analyses revealed that the greatest benefit of lovastatin treatment was evident in those patients with the higher risk factors for CHD. The results of AFCAPS/TexCAPS, the cohort studied, and the population deriving the benefit of therapy should be appropriately reflected in the labeling.

Clinical Pharmacology, Clinical Studies

The introductory statement here is vague and misleading with the deletion of quantitative terms such as **high** LDL-C and **low** HDL-C associated with coronary heart disease and the inclusion of "a significant number of coronary events occur in individuals who do not have a high total cholesterol and LDL-C". The presence of LDL-C and HDL-C alone is not associated with CHD but rather, is a result of their levels and other known risk factors which contribute to the development of CHD.

The following revision should be made to better define this subgroup of patients who may benefit from therapy with lovastatin and establish a rationale for the conduct of AFCAPS/TexCAPS.

DRAFT LABELING

[redacted]

A description of AFCAPS/TexCAPS in the second paragraph of this section is redundant as this is further detailed under clinical studies. This second paragraph should not be included in the revised label and the results of the trial can be outlined in a subheading under the *Clinical Studies* section. In this section reference to NHANES should not be included but replaced with a description of the cohort as follows:

DRAFT LABELING

[redacted]

The description of the lipid parameter should be based on either the actual range and observed mean values obtained in the trial or present the entry lipid criteria. The label should state that approximately 50% of the participants treated with lovastatin required