

treatment from AFCAPS/TexCAPS could not be made to this reference population. Indeed, the AFCAPS/TexCAPS cohort was 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 and the cohort studied 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. Although coronary events are reported in individuals without exceedingly elevated TC and LDL-C levels the sponsor's proposed statement leads the clinician to ponder: *What is a significant number of coronary events? What qualifies as a high TC or LDL-C? Should all patients with average to slightly elevated cholesterol levels be treated irrespective of other CHD risk factors?*

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

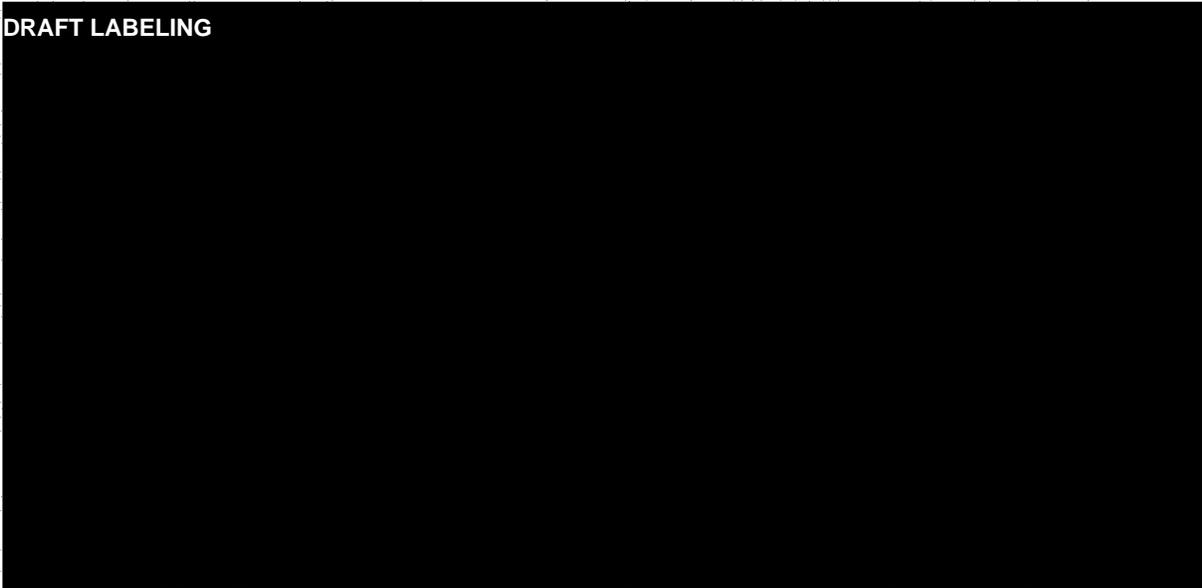
A description of AFCAPS/TexCAPS in the second paragraph of this section does appear redundant as this is further detailed under clinical studies although a similar description is found for the 4S study in the simvastatin label. An abbreviated description can be placed here without reference to NHANES data.

DRAFT LABELING

The results of the study can be further detailed in a subheading under the *Clinical Studies* section. In this section reference to NHANES should be replaced by the actual lipid inclusion criteria and the AFCAPS/TexCAPS mean lipid levels. Use of the statement, "mean levels of the US reference population", does not adequately describe the study population in which the benefits of lovastatin was studied. Reference should be made to the CHD risk factors present in this cohort because the benefit of lovastatin

therapy was highest in this group. The first 2 paragraphs on the AFCAPS/TexCAPS clinical study should be replaced with:

DRAFT LABELING

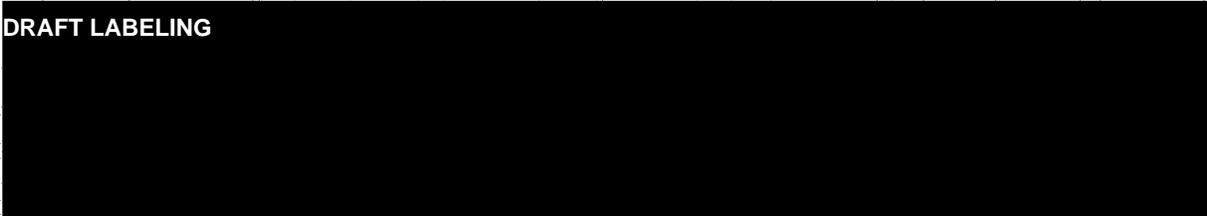


The third paragraph describing the AFCAPS/TexCAPS clinical study is acceptable **except** any reference to benefits of therapy to women and diabetics should be deleted because data from these subgroups were inconclusive. The figure used to illustrate effects of treatment on primary endpoints should use proportion surviving compared over months of study as this is consistent with other statin labels.

Indications and Usage

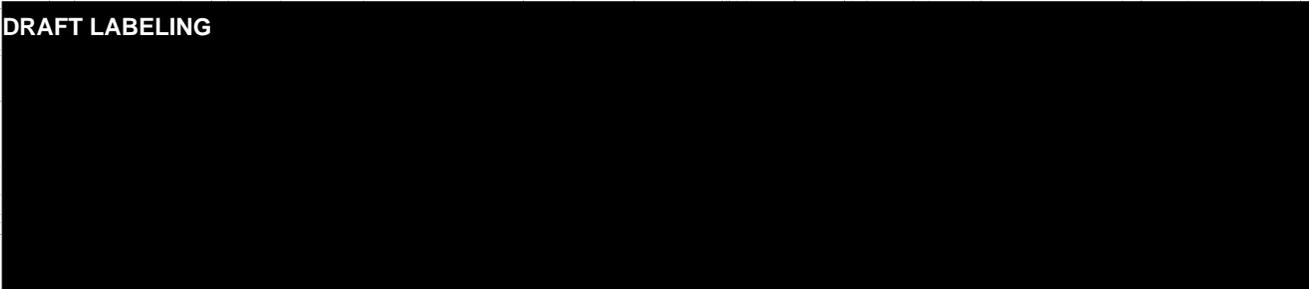
The introductory paragraph is confusing with respect to describing the individuals for which lovastatin is indicated. A statement on the drug's use as part of a treatment strategy to lower TC and LDL-C is repetitive as this is mentioned in the subsequent subheadings, *Coronary Heart Disease* and *Hypercholesterolemia*. The following revision will more adequately describe the population for which lovastatin is indicated and resembles the simvastatin label.

DRAFT LABELING



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

DRAFT LABELING



(See CLINICAL PHARMACOLOGY, Clinical Studies)

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.

The subheading, *Hypercholesterolemia*, can be abbreviated since part of this paragraph was already stated in the introductory statement.

DRAFT LABELING

Warnings

The changes proposed by the sponsor for liver function tests are acceptable **except** the statement, "Patients titrated to the 80 mg dose..." should be changed to:

DRAFT LABELING

Dosage and Administration

The LDL-C treatment goal in AFCAPS/TexCAPS was 110 mg/dL. Based on NCEP guidelines patients without a history of CHD with < 2 risk factors the LDL-C treatment goal is <160 mg/dL and in those patients with ≥2 risk factors the LDL-C treatment goal is <130 mg/dL. In AFCAPS/TexCAPS, only 16.6% of the cohort qualified for initiation of drug therapy based on NCEP recommendations. However, 63% of the cohort had ≥2 risk factors and the benefit of lovastatin treatment was predominant in this group (risk reduction 42%, p<0.0001 versus 17%, p=0.44 in patients with < 2 risk factors). An LDL-C treatment goal of 110 mg/dL for this cohort corresponds to NCEP recommendations and hence **the reference to NCEP guidelines should not be deleted** in the AFCAPS/TexCAPS label.

Other Labeling Changes Unrelated to AFCAPS/TexCAPS

- *deletion of warnings on interactions with mibefradil as this drug has been withdrawn from the market*
- *insertion of section on increased lovastatin drug levels when taken with grapefruit juice since the latter is a known inhibitor of cytochrome P450 isoform 3A4*

APPEARS THIS WAY ON ORIGINAL