CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-766/S052

MEDICAL REVIEW(S)

TEAM LEADER'S MEMO ON LABELING SUPPLEMENT

NDA #: 19-766/supplement 052 (previously submitted as — on 11/30/00 but this application was administratively split ——— 052 ———————

Product: Simvastatin (Zocor)
Sponsor: Merck Research Laboratories
Date of Submission: November 30, 2000

Introduction

This labeling supplement proposes to change the CLINICAL PHARMACOLOGYsection of the label from the following statement:

"Epidemiological studies have established that high LDL-C, low HDL-C,and high plasma TGs are risk factors for CHD"

to:

"Epidemiological studies have established that elevated plasma levels of total-C, LDL-C and Apo B promote human atherosclerosis and are risk factors for developing CVD while increased levels of HDL-C ——— and its transport complex, Apo A-1, are associated with decreased cardiovascular risk."

Review of Submitted Data

Clinical Pharmacology Revisions

The sponsor provided 4 published articles to support the revisions under this section of the label. They are:

1. Castelli WP et al. Incidence of CHD and Lipoprotein Cholesterol Levels. *JAMA* 1986;256:2835-2838
2. Pereira MA et al. The Family Risk Score for CHD: Associations with Lipids, Lipoproteins, and Body Habitus in a Middle-Aged Bi-racial Cohort: The ARIC Study. *Ann Epidemiol* 2000; 10:239-245.
3. Luc G et al. Interstitial Fluid Apolipoprotein A-II: An Association with the Occurrence of MI. *Atherosclerosis* 127(1996):131-137
4. Gordon DJ et al. HDL-C and CVD. Four Prospective American Studies. *Circulation* 1989;79:8-15.

Articles #1 and 4 evaluated the role of HDL-C and the development of CHD. One was in the Framingham Cohort and the other compared results from the Framingham Study, Lipid Research Clinics Prevalence Mortality Follow-up Study, LRC-CPPT, and MRFIT. Article #2 evaluated the Family Risk Scores (FRS) for CHD from the Atherosclerosis Risk In Communities Study Cohort in relation to other risk factors: BMI, WHR, HDL, LDL, TG, and Lp(a). The results of these studies demonstrate the increase risk of CVD associated with low HDL-C levels.

Article #3 was submitted to support the role of Apo A-1 on the risk of CVD. Apo A-1 is a major lipoprotein associated with HDL. Overexpression of this apolipoprotein in transgenic mice results in increased HDL-C levels and Apo A-1 levels. These animals demonstrate decreased fatty streak lesions in the aorta after receiving high fat diets. In

this case-control study, recent survivors of a myocardial infarction (MI) were compared to age-matched controls to evaluate the differences in lipids and apolipoproteins levels in interstitial fluid between MI patients and controls. In addition to analyses of interstitial fluids, blood samples for cholesterol, triglycerides, apo A-I, A-II, A-IV, LpA-I, and LpA-I:A-II, HDL-C, and VLDL-C were also measured.

The mean concentrations of TG, VLDL-C, and apo B lipoproteins were significantly higher in cases versus controls. In contrast, the mean concentrations of HDL-C and Apo A-I were significantly lower in survivors of MI versus controls. These results were observed after adjustments for age, BMI, alcohol intake, and smoking. The mean plasma Apo A-1 level was 137.5 mg/dL in cases versus 153.9 mg/dL in controls; p=0.0001).

The 4 reference articles submitted with this application further support the inverse relationship between HDL-C and apo A-I lipoproteins and the risk of atherosclerosis.

Recommendations

The modification of the statement describing the role certain lipids and their associated lipoproteins on the risk of atherosclerosis to include HDL-C and apolipoprotein A-I as inversely affecting cardiovascular disease is acceptable. However, the sponsor should delete the parenthetical comment, ———— to maintain consistency with other statin labels.

The following labeling change is acceptable for approval of this supplemental application:

"*Epidemiological studies have established that elevated plasma levels of total-C, LDL-C and Apo B promote human atherosclerosis and are risk factors for developing CVD while increased levels of HDL-C and its transport complex, Apo A-1, are associated with decreased cardiovascular risk.*"

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