# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

***APPLICATION NUMBER:***

# NDA 19-766/S-058

***Trade Name:*** Zocor Tablets

***Generic Name:*** Simvastatin

***Sponsor:*** Merck & Co., Inc.

***Approval Date:*** April 16, 2003

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# NDA 19-766/S-058

## CONTENTS

| Reviews / Information Included in this NDA Review. | |
|---|---|
| Approval Letter | X |
| Approvable Letter | |
| Final Printed Labeling | X |
| Medical Review(s) | X |
| Chemistry Review(s) | X |
| EA/FONSI | X |
| Pharmacology Review(s) | |
| Statistical Review(s) | X |
| Microbiology Review(s) | |
| Clinical Pharmacology/ Biopharmaceutics Review(s) | |
| Administrative and Correspondence Document(s) | X |

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# NDA 19-766/S-058

# APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-766/S-058

Merck & Co., Inc.
Attention: Michael C. Elia, Ph.D., DABT
Senior Director, Regulatory Affairs
Sumneytown Pike, P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Elia:

Please refer to your supplemental new drug application dated June 18, 2002, received June 19, 2002 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zocor (simvastatin) Tablets.

We acknowledge receipt of your submissions dated September 16 and 23, and November 22, 2002, January 31, February 3, and April 10 (3), 2003.

This supplemental new drug application provides for a new indication, based on the results of the Heart Protection Study (HPS), for the use of simvastatin in patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease to reduce the risk of total mortality by reducing coronary death, to reduce the risk of non-fatal myocardial infarction and stroke, and to reduce the need for coronary and non-coronary revascularization procedures. In addition, this supplemental application provides for changes to the CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of the ZOCOR package insert.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted April 10, 2003)(copy enclosed).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-766 /S-058." Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Margaret Simoneau, R.Ph., Regulatory Project Manager, at (301) 827-6411.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/

David Orloff
4/16/03 02:48:16 PM

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# NDA 19-766/S-058

# APPROVED LABELING

**MERCK & CO., INC.**
Whitehouse Station, NJ 08889, USA

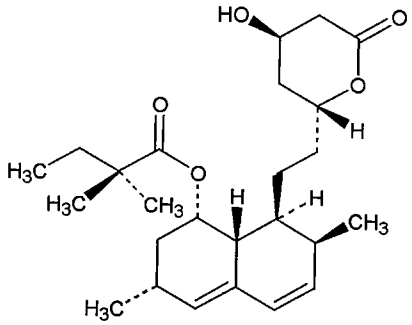
~~782544X~~

TABLETS
# ZOCOR®
## (SIMVASTATIN)

### DESCRIPTION

ZOCOR[1] (simvastatin) is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1*S*-[1α,3α,7β,8β(2*S**,4*S**),-8aβ]]. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. Its structural formula is:




Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol.

Tablets ZOCOR for oral administration contain either 5 mg, 10 mg, 20 mg, 40 mg or 80 mg of simvastatin and the following inactive ingredients: cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, lactose, magnesium stearate, starch, talc, titanium dioxide and other ingredients. Butylated hydroxyanisole is added as a preservative.

### CLINICAL PHARMACOLOGY

The involvement of low-density lipoprotein cholesterol (LDL-C) in atherogenesis has been well-documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological studies have established that elevated plasma levels of total cholesterol (total-C), LDL-C, and apolipoprotein B (Apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of high-density lipoprotein cholesterol (HDL-C) and its transport complex, Apo A-I, are associated with decreased cardiovascular risk. High plasma triglycerides (TG) and cholesterol-enriched TG-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. Elevated plasma TG are frequently found in a triad with low HDL-C and small LDL particles, as well as in association with non-lipid metabolic risk factors for CHD. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

In the Scandinavian Simvastatin Survival Study (4S), the effect of improving lipoprotein levels with ZOCOR on total mortality was assessed in 4,444 patients with CHD and baseline total cholesterol (total-C) 212-309 mg/dL (5.5-8.0 mmol/L). The patients were followed for a median of 5.4 years. In this multicenter, randomized, double-blind, placebo-controlled study, ZOCOR significantly reduced the risk of mortality by 30% (11.5% vs 8.2%, placebo vs ZOCOR); of CHD mortality by 42% (8.5% vs 5.0%); and of having a

[1] Registered trademark of MERCK & CO., Inc.

hospital-verified non-fatal myocardial infarction by 37% (19.6% vs 12.9%). Furthermore, ZOCOR significantly reduced the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37% (17.2% vs 11.4%) [see CLINICAL PHARMACOLOGY, *Clinical Studies*].

ZOCOR has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very-low-density lipoprotein (VLDL) and is catabolized predominantly by the high-affinity LDL receptor. The mechanism of the LDL-lowering effect of ZOCOR may involve both reduction of VLDL cholesterol concentration, and induction of the LDL receptor, leading to reduced production and/or increased catabolism of LDL-C. Apo B also falls substantially during treatment with ZOCOR. As each LDL particle contains one molecule of Apo B, and since in patients with predominant elevations in LDL-C (without accompanying elevation in VLDL) little Apo B is found in other lipoproteins, this strongly suggests that ZOCOR does not merely cause cholesterol to be lost from LDL, but also reduces the concentration of circulating LDL particles. In addition, ZOCOR reduces VLDL and TG and increases HDL-C. The effects of ZOCOR on Lp(a), fibrinogen, and certain other independent biochemical risk markers for CHD are unknown.

ZOCOR is a specific inhibitor of HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate. The conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol.

*Pharmacokinetics*

Simvastatin is a lactone that is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the β-hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin.

Following an oral dose of $^{14}C$-labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug. Plasma concentrations of total radioactivity (simvastatin plus $^{14}C$-metabolites) peaked at 4 hours and declined rapidly to about 10% of peak by 12 hours postdose. Absorption of simvastatin, estimated relative to an intravenous reference dose, in each of two animal species tested, averaged about 85% of an oral dose. In animal studies, after oral dosing, simvastatin achieved substantially higher concentrations in the liver than in non-target tissues. Simvastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of simvastatin (estimated to be > 60% in man), the availability of drug to the general circulation is low. In a single-dose study in nine healthy subjects, it was estimated that less than 5% of an oral dose of simvastatin reaches the general circulation as active inhibitors. Following administration of simvastatin tablets, the coefficient of variation, based on between-subject variability, was approximately 48% for the area under the concentration-time curve (AUC) for total inhibitory activity in the general circulation.

Both simvastatin and its β-hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins. Animal studies have not been performed to determine whether simvastatin crosses the blood-brain and placental barriers. However, when radiolabeled simvastatin was administered to rats, simvastatin-derived radioactivity crossed the blood-brain barrier.

The major active metabolites of simvastatin present in human plasma are the β-hydroxyacid of simvastatin and its 6′-hydroxy, 6′-hydroxymethyl, and 6′-exomethylene derivatives. Peak plasma concentrations of both active and total inhibitors were attained within 1.3 to 2.4 hours postdose. While the recommended therapeutic dose range is 5 to 80 mg/day, there was no substantial deviation from linearity of AUC of inhibitors in the general circulation with an increase in dose to as high as 120 mg. Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before an American Heart Association recommended low-fat meal.

In a study including 16 elderly patients between 70 and 78 years of age who received ZOCOR 40 mg/day, the mean plasma level of HMG-CoA reductase inhibitory activity was increased approximately 45% compared with 18 patients between 18-30 years of age. Clinical study experience in the elderly (n=1522), suggests that there were no overall differences in safety between elderly and younger patients (see PRECAUTIONS, *Geriatric Use*).

Kinetic studies with another reductase inhibitor, having a similar principal route of elimination, have suggested that for a given dose level higher systemic exposure may be achieved in patients with severe renal insufficiency (as measured by creatinine clearance).

In a study of 12 healthy volunteers, simvastatin at the 80-mg dose had no effect on the metabolism of the probe cytochrome P450 isoform 3A4 (CYP3A4) substrates midazolam and erythromycin. This

indicates that simvastatin is not an inhibitor of CYP3A4, and, therefore, is not expected to affect the plasma levels of other drugs metabolized by CYP3A4.

The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Potent inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*).

Simvastatin is a substrate for CYP3A4 (see PRECAUTIONS, *Drug Interactions*). Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma concentrations of drugs metabolized by CYP3A4. In one study[2], 10 subjects consumed 200 mL of double-strength grapefruit juice (one can of frozen concentrate diluted with one rather than 3 cans of water) three times daily for 2 days and an additional 200 mL double-strength grapefruit juice together with and 30 and 90 minutes following a single dose of 60 mg simvastatin on the third day. This regimen of grapefruit juice resulted in mean increases in the concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [measured using a radioenzyme inhibition assay both before (for active inhibitors) and after (for total inhibitors) base hydrolysis] of 2.4-fold and 3.6-fold, respectively, and of simvastatin and its β-hydroxyacid metabolite [measured using a chemical assay — liquid chromatography/tandem mass spectrometry] of 16-fold and 7-fold, respectively. In a second study, 16 subjects consumed one 8 oz glass of single-strength grapefruit juice (one can of frozen concentrate diluted with 3 cans of water) with breakfast for 3 consecutive days and a single dose of 20 mg simvastatin in the evening of the third day. This regimen of grapefruit juice resulted in a mean increase in the plasma concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [using a validated enzyme inhibition assay different from that used in the first[2] study, both before (for active inhibitors) and after (for total inhibitors) base hydrolysis] of 1.13-fold and 1.18-fold, respectively, and of simvastatin and its β-hydroxyacid metabolite [measured using a chemical assay — liquid chromatography/tandem mass spectrometry] of 1.88-fold and 1.31-fold, respectively. The effect of amounts of grapefruit juice between those used in these two studies on simvastatin pharmacokinetics has not been studied.

*Clinical Studies in Adults*

*Reductions in Risk of CHD Mortality and Cardiovascular Events*

In 4S, the effect of therapy with ZOCOR on total mortality was assessed in 4,444 patients with CHD and baseline total cholesterol 212-309 mg/dL (5.5-8.0 mmol/L). In this multicenter, randomized, double-blind, placebo-controlled study, patients were treated with standard care, including diet, and either ZOCOR 20-40 mg/day (n=2,221) or placebo (n=2,223) for a median duration of 5.4 years. After six weeks of treatment with ZOCOR the median ($25^{th}$ and $75^{th}$ percentile) changes in LDL-C, TG, and HDL-C were -39% (-46, -31%), -19% (-31, 0%), and 6% (-3, 17%). Over the course of the study, treatment with ZOCOR led to mean reductions in total-C, LDL-C and TG of 25%, 35%, and 10%, respectively, and a mean increase in HDL-C of 8%. ZOCOR significantly reduced the risk of mortality by 30%, (p=0.0003, 182 deaths in the ZOCOR group vs 256 deaths in the placebo group). The risk of CHD mortality was significantly reduced by 42%, (p=0.00001, 111 vs 189 deaths). There was no statistically significant difference between groups in non-cardiovascular mortality. ZOCOR also significantly decreased the risk of having major coronary events (CHD mortality plus hospital-verified and silent non-fatal myocardial infarction [MI]) by 34%, (p<0.00001, 431 vs 622 patients with one or more events). The risk of having a hospital-verified non-fatal MI was reduced by 37%. ZOCOR significantly reduced the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37%, (p<0.00001, 252 vs 383 patients). Furthermore, ZOCOR significantly reduced the risk of fatal plus non-fatal cerebrovascular events (combined stroke and transient ischemic attacks) by 28% (p=0.033, 75 vs 102 patients). ZOCOR reduced the risk of major coronary events to a similar extent across the range of baseline total and LDL cholesterol levels. Because there were only 53 female deaths, the effect of ZOCOR on mortality in women could not be adequately assessed. However, ZOCOR significantly lessened the risk of having major coronary events by 34% (60 vs 91 women with one or more event). The randomization was stratified by angina alone (21% of each treatment group) or a previous MI. Because there were only 57 deaths among the patients with angina alone at baseline, the effect of ZOCOR on mortality in this subgroup could not be adequately assessed. However, trends in reduced coronary mortality, major coronary events and revascularization procedures were consistent between this group and the total study cohort. Additionally, in this study, 1,021 of the patients were 65 and older. Cholesterol reduction with simvastatin resulted in similar decreases in relative risk for total mortality, CHD mortality, and major coronary events in these elderly patients, compared with younger patients.

[2] Lilja JJ, Kivisto KT, Neuvonen PJ. Clin Pharmacol Ther 1998;64(5):477-83.

The Heart Protection Study (HPS) was a large, multi-center, placebo-controlled, double-blind study with a mean duration of 5 years conducted in 20,536 patients (10,269 on ZOCOR 40 mg and 10,267 on placebo). Patients were allocated to treatment using a covariate adaptive method[3] which took into account the distribution of 10 important baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients had a mean age of 64 years (range 40-80 years), were 97% Caucasian and were at high risk of developing a major coronary event because of existing coronary heart disease (65%), diabetes (Type 2, 26%; Type 1, 3%), history of stroke or other cerebrovascular disease (16%), peripheral vessel disease (33%), or hypertension in males 65 years of age and older (6%). At baseline, 3,421 patients (17%) had LDL-C levels below 100 mg/dL, of whom 953 (9%) had LDL-C levels below 80 mg/dL; 7,068 patients (34%) had levels between 100 and 130 mg/dL; and 10,047 patients (49%) had levels greater than 130 mg/dL.

The HPS results showed that ZOCOR 40 mg/day significantly reduced: total and CHD mortality; non-fatal myocardial infarctions, stroke, and revascularization procedures (coronary and non-coronary) (see Table 1).

TABLE 1
Summary of Heart Protection Study Results

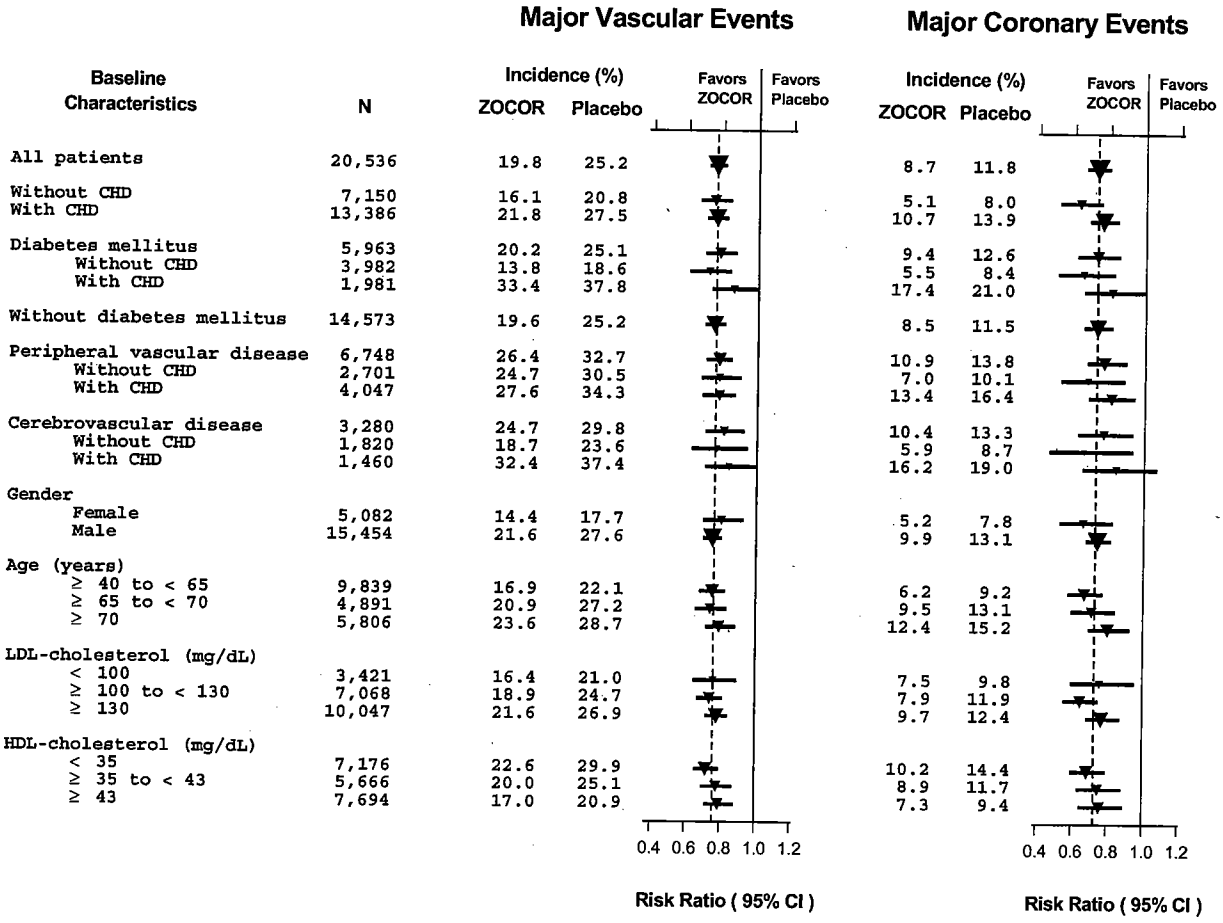
| Endpoint | ZOCOR (N=10,269) n (%)† | Placebo (N=10,267) n (%)† | Risk Reduction (%) (95% CI) | p-Value |
|---|---|---|---|---|
| **Primary** | | | | |
| Mortality | 1,328 (12.9) | 1,507 (14.7) | 13 (6-19) | p=0.0003 |
| CHD mortality | 587 (5.7) | 707 (6.9) | 18 (8-26) | p=0.0005 |
| **Secondary** | | | | |
| Non-fatal MI | 357 (3.5) | 574 (5.6) | 38 (30-46) | p<0.0001 |
| Stroke | 444 (4.3) | 585 (5.7) | 25 (15-34) | p<0.0001 |
| **Tertiary** | | | | |
| Coronary revascularization | 513 (5) | 725 (7.1) | 30 (22-38) | p<0.0001 |
| Peripheral and other non-coronary revascularization | 450 (4.4) | 532 (5.2) | 16 (5-26) | p=0.006 |

† n = number of patients with indicated event

Two composite endpoints were defined in order to have sufficient events to assess relative risk reductions across a range of baseline characteristics (see Figure 1). A composite of major coronary events (MCE) was comprised of CHD mortality and non-fatal MI (analyzed by time-to-first event; 898 patients treated with ZOCOR had events and 1,212 patients on placebo had events). A composite of major vascular events (MVE) was comprised of MCE, stroke and revascularization procedures including coronary, peripheral and other non-coronary procedures (analyzed by time-to-first event; 2,033 patients treated with ZOCOR had events and 2,585 patients on placebo had events). Significant relative risk reductions were observed for both composite endpoints (27% for MCE and 24% for MVE, p<0.0001). Furthermore, treatment with ZOCOR produced significant relative risk reductions for all components of the composite endpoints. The risk reductions produced by ZOCOR in both MCE and MVE were evident and consistent regardless of cardiovascular disease related medical history at study entry (i.e., CHD alone; or peripheral vascular disease, cerebrovascular disease, diabetes or treated hypertension, with or without CHD), gender, age, creatinine levels up to the entry limit of 2.3 mg/dL, baseline levels of LDL-C, HDL-C, apolipoprotein B and A-1, baseline concomitant cardiovascular medications (i.e., aspirin, beta blockers, or calcium channel blockers), smoking status, alcohol intake, or obesity. Diabetics showed risk reductions for MCE and MVE due to ZOCOR treatment regardless of baseline HbA1c levels or obesity with the greatest effects seen for diabetics without CHD.

[3] D.R. Taves, Minimization: a new method of assigning patients to treatment and control groups. Clin. Pharmacol. Ther. **15** (1974), pp. 443-453

Figure 1
The Effects of Treatment with ZOCOR on Major Vascular Events and Major Coronary Events in HPS




N= number of patients in each subgroup. The inverted triangles are point estimates of the relative risk, with their 95% confidence intervals represented as a line. The area of a triangle is proportional to the number of patients with MVE or MCE in the subgroup relative to the number with MVE or MCE, respectively, in the entire study population. The vertical solid line represents a relative risk of one. The vertical dashed line represents the point estimate of relative risk in the entire study population.

*Angiographic Studies*

In the Multicenter Anti-Atheroma Study, the effect of simvastatin on atherosclerosis was assessed by quantitative coronary angiography in hypercholesterolemic patients with coronary heart disease. In this randomized, double-blind, controlled study, patients were treated with simvastatin 20 mg/day or placebo. Angiograms were evaluated at baseline, two and four years. The co-primary study endpoints were mean change per-patient in minimum and mean lumen diameters, indicating focal and diffuse disease, respectively. Simvastatin significantly slowed the progression of lesions as measured in the Year 4 angiogram by both parameters, as well as by change in percent diameter stenosis. In addition, simvastatin significantly decreased the proportion of patients with new lesions and with new total occlusions.

*Modifications of Lipid Profiles*

*Primary Hypercholesterolemia (Fredrickson type IIa and IIb)*

ZOCOR has been shown to be highly effective in reducing total-C and LDL-C in heterozygous familial and non-familial forms of hypercholesterolemia and in mixed hyperlipidemia. A marked response was seen within 2 weeks, and the maximum therapeutic response occurred within 4-6 weeks. The response was maintained during chronic therapy. Furthermore, improving lipoprotein levels with ZOCOR improved survival in patients with CHD and hypercholesterolemia treated with 20-40 mg/day for a median of 5.4 years.

In a multicenter, double-blind, placebo-controlled, dose-response study in patients with familial or non-familial hypercholesterolemia, ZOCOR given as a single dose in the evening (the recommended dosing) was similarly effective as when given on a twice-daily basis. ZOCOR consistently and significantly

decreased total-C, LDL-C, total-C/HDL-C ratio, and LDL-C/HDL-C ratio. ZOCOR also decreased TG and increased HDL-C.

The results of studies depicting the mean response to simvastatin in patients with primary hypercholesterolemia and combined (mixed) hyperlipidemia are presented in Table 2.

TABLE 2
Mean Response in Patients with Primary Hypercholesterolemia and Combined (mixed) Hyperlipidemia
(Mean Percent Change from Baseline After 6 to 24 Weeks)

| TREATMENT | N | TOTAL-C | LDL-C | HDL-C | TG† |
|---|---|---|---|---|---|
| Lower Dose Comparative Study (Mean % Change at Week 6) | | | | | |
| **ZOCOR** 5 mg q.p.m. | 109 | -19 | -26 | 10 | -12 |
| **ZOCOR** 10 mg q.p.m. | 110 | -23 | -30 | 12 | -15 |
| Scandinavian Simvastatin Survival Study (Mean % Change at Week 6) | | | | | |
| Placebo | 2223 | -1 | -1 | 0 | -2 |
| **ZOCOR** 20 mg q.p.m. | 2221 | -28 | -38 | 8 | -19 |
| Upper Dose Comparative Study (Mean % Change Averaged at Weeks 18 and 24) | | | | | |
| **ZOCOR** 40 mg q.p.m. | 433 | -31 | -41 | 9 | -18 |
| **ZOCOR** 80 mg q.p.m. | 664 | -36 | -47 | 8 | -24 |
| Multi-Center Combined Hyperlipidemia Study (Mean % Change at Week 6) | | | | | |
| Placebo | 125 | 1 | 2 | 3 | -4 |
| **ZOCOR** 40 mg q.p.m. | 123 | -25 | -29 | 13 | -28 |
| **ZOCOR** 80 mg q.p.m. | 124 | -31 | -36 | 16 | -33 |

† median percent change

In the Upper Dose Comparative Study, the mean reduction in LDL-C was 47% at the 80-mg dose. Of the 664 patients randomized to 80 mg, 475 patients with plasma TG ≤ 200 mg/dL had a median reduction in TG of 21%, while in 189 patients with TG > 200 mg/dL, the median reduction in TG was 36%. In these studies, patients with TG > 350 mg/dL were excluded.

In the Multi-Center Combined Hyperlipidemia Study, a randomized, 3-period crossover study, 130 patients with combined hyperlipidemia (LDL-C>130 mg/dL and TG: 300-700 mg/dL) were treated with placebo, ZOCOR 40, and 80 mg/day for 6 weeks. In a dose-dependent manner ZOCOR 40 and 80 mg/day, respectively, decreased mean LDL-C by 29 and 36% (placebo: +2%) and median TG levels by 28 and 33% (placebo: 4%), and increased mean HDL-C by 13 and 16% (placebo: 3%) and apolipoprotein A-I by 8 and 11% (placebo: 4%).

*Hypertriglyceridemia (Fredrickson type IV)*

The results of a subgroup analysis in 74 patients with type IV hyperlipidemia from a 130-patient double-blind, placebo-controlled, 3-period crossover study are presented in Table 3. The median baseline values (mg/dL) for the patients in this study were: total-C = 254, LDL-C = 135, HDL-C = 36, TG = 404, VLDL-C = 83, and non-HDL-C = 215.

TABLE 3
Six-week, Lipid-lowering Effects of Simvastatin in Type IV Hyperlipidemia
Median Percent Change (25th and 75th percentile) from Baseline

| TREATMENT | N | Total-C | LDL-C | HDL-C | TG | VLDL-C | Non-HDL-C |
|---|---|---|---|---|---|---|---|
| Placebo | 74 | +2 (-7, +7) | +1 (-8, +14) | +3 (-3, +10) | -9 (-25, +13) | -7 (-25, +11) | +1 (-9, +8) |
| ZOCOR 40 mg/day | 74 | -25 (-34, -19) | -28 (-40, -17) | +11 (+5, +23) | -29 (-43, -16) | -37 (-54, -23) | -32 (-42, -23) |
| ZOCOR 80 mg/day | 74 | -32 (-38, -24) | -37 (-46, -26) | +15 (+5, +23) | -34 (-45, -18) | -41 (-57, -28) | -38 (-49, -32) |

*Dysbetalipoproteinemia (Fredrickson type III)*

The results of a subgroup analysis in 7 patients with type III hyperlipidemia (dysbetalipoproteinemia) (apo E2/2) (VLDL-C/TG>0.25) from a 130-patient double-blind, placebo-controlled, 3-period crossover study are presented in Table 4. In this study the median baseline values (mg/dL) were: total-C = 324, LDL-C = 121, HDL-C = 31, TG = 411, VLDL-C = 170, and non-HDL-C = 291.

TABLE 4
Six-week, Lipid-lowering Effects of Simvastatin in Type III Hyperlipidemia
Median Percent Change (min,max) from Baseline

| TREATMENT | N | Total-C | LDL-C + IDL | HDL-C | TG | VLDL-C+IDL | Non-HDL-C |
|---|---|---|---|---|---|---|---|
| Placebo | 7 | -8 (-24,+34) | -8 (-27,+23) | -2 (-21,+16) | +4 (-22,+90) | -4 (-28,+78) | -8 (-26,-39) |
| ZOCOR 40 mg/day | 7 | -50 (-66,-39) | -50 (-60,-31) | +7 (-8,+23) | -41 (-74,-16) | -58 (-90,-37) | -57 (-72,-44) |
| ZOCOR 80 mg/day | 7 | -52 (-55,-41) | -51 (-57,-28) | +7 (-5,+29) | -38 (-58,+2) | -60 (-72,-39) | -59 (-61,-46) |

*Homozygous Familial Hypercholesterolemia*

In a controlled clinical study, 12 patients 15-39 years of age with homozygous familial hypercholesterolemia received simvastatin 40 mg/day in a single dose or in 3 divided doses, or 80 mg/day in 3 divided doses. Eleven of the 12 patients had reductions in LDL-C. In those patients with reductions, the mean LDL-C changes for the 40- and 80-mg doses were 14% (range 8% to 23%, median 12%) and 30% (range 14% to 46%, median 29%), respectively. One patient had an increase of 15% in LDL-C. Another patient with absent LDL-C receptor function had an LDL-C reduction of 41% with the 80-mg dose.

*Endocrine Function*

In clinical studies, simvastatin did not impair adrenal reserve or significantly reduce basal plasma cortisol concentration. Small reductions from baseline in basal plasma testosterone in men were observed in clinical studies with simvastatin, an effect also observed with other inhibitors of HMG-CoA reductase and the bile acid sequestrant cholestyramine. There was no effect on plasma gonadotropin levels. In a placebo-controlled 12-week study there was no significant effect of simvastatin 80 mg on the plasma testosterone response to human chorionic gonadotropin (hCG). In another 24-week study, simvastatin 20-40 mg had no detectable effect on spermatogenesis. In 4S, in which 4,444 patients were randomized to simvastatin 20-40 mg/day or placebo for a median duration of 5.4 years, the incidence of male sexual adverse events in the two treatment groups was not significantly different. Because of these factors, the small changes in plasma testosterone are unlikely to be clinically significant. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown.

*Clinical Studies in Adolescents*

In a double-blind, placebo-controlled study, 175 patients (99 adolescent boys and 76 post-menarchal girls) 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (heFH) were randomized to simvastatin (n=106) or placebo (n=67) for 24 weeks (base study). Inclusion in the study required a baseline LDL-C level between 160 and 400 mg/dL and at least one parent with an LDL-C level >189 mg/dL. The dosage of simvastatin (once daily in the evening) was 10 mg for the first 8 weeks, 20 mg for the second 8 weeks, and 40 mg thereafter. In a 24-week extension, 144 patients elected to continue therapy and received simvastatin 40 mg or placebo.

ZOCOR significantly decreased plasma levels of total-C, LDL-C, and Apo B (see Table 5). Results from the extension at 48 weeks were comparable to those observed in the base study.

TABLE 5
Lipid-lowering Effects of Simvastatin in Adolescent Patients with Heterozygous Familial Hypercholesterolemia
(Mean Percent Change from Baseline)

| Dosage | Duration | N | | Total-C | LDL-C | HDL-C | TG† | Apo B |
|---|---|---|---|---|---|---|---|---|
| Placebo | 24 Weeks | 67 | % Change from Baseline (95% CI) | 1.6 (-2.2, 5.3) | 1.1 (-3.4, 5.5) | 3.6 (-0.7, 8.0) | -3.2 (-11.8, 5.4) | -0.5 (-4.7, 3.6) |
| | | | Mean baseline, mg/dL (SD) | 278.6 (51.8) | 211.9 (49.0) | 46.9 (11.9) | 90.0 (50.7) | 186.3 (38.1) |
| ZOCOR | 24 Weeks | 106 | % Change from Baseline (95% CI) | -26.5 (-29.6, -23.3) | -36.8 (-40.5, -33.0) | 8.3 (4.6, 11.9) | -7.9 (-15.8, 0.0) | -32.4 (-35.9, -29.0) |
| | | | Mean baseline, mg/dL (SD) | 270.2 (44.0) | 203.8 (41.5) | 47.7 (9.0) | 78.3 (46.0) | 179.9 (33.8) |

†median percent change

After 24 weeks of treatment, the mean achieved LDL-C value was 124.9 mg/dL (range: 64.0-289.0 mg/dL) in the Zocor 40 mg group compared to 207.8 mg/dL (range: 128.0-334.0 mg/dL) in the placebo group.

The safety and efficacy of doses above 40 mg daily have not been studied in children with heterozygous familial hypercholesterolemia. The long-term efficacy of simvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

## INDICATIONS AND USAGE

Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

In patients with CHD or at high risk of CHD, ZOCOR can be started simultaneously with diet.

*Reductions in Risk of CHD Mortality and Cardiovascular Events*

In patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, ZOCOR is indicated to:

- Reduce the risk of total mortality by reducing CHD deaths.
- Reduce the risk of non-fatal myocardial infarction and stroke.
- Reduce the need for coronary and non-coronary revascularization procedures.

*Patients with Hypercholesterolemia Requiring Modifications of Lipid Profiles*

ZOCOR is indicated to:

- Reduce elevated total-C, LDL-C, Apo B, and TG, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson types IIa and IIb[4]).
- Treat patients with hypertriglyceridemia (Fredrickson type IV hyperlipidemia).
- Treat patients with primary dysbetalipoproteinemia (Fredrickson type III hyperlipidemia).
- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

[4] Classification of Hyperlipoproteinemias

| Type | Lipoproteins elevated | Lipid Elevations major | minor |
|---|---|---|---|
| I (rare) | chylomicrons | TG | ↑→C |
| IIa | LDL | C | — |
| IIb | LDL, VLDL | C | TG |
| III (rare) | IDL | C/TG | — |
| IV | VLDL | TG | ↑→C |
| V (rare) | chylomicrons, VLDL | TG | ↑→C |

C = cholesterol, TG = triglycerides,
LDL = low-density lipoprotein,
VLDL = very-low-density lipoprotein,
IDL = intermediate-density lipoprotein.

*Adolescent Patients with Heterozygous Familial Hypercholesterolemia (HeFH)*

ZOCOR is indicated as an adjunct to diet to reduce total-C, LDL-C, and Apo B levels in adolescent boys and girls who are at least one year post-menarche, 10-17 years of age, with heterozygous familial hypercholesterolemia, if after an adequate trial of diet therapy the following findings are present:

1. LDL cholesterol remains ≥190 mg/dL; or
2. LDL cholesterol remains ≥160 mg/dL and

- There is a positive family history of premature cardiovascular disease (CVD) or
- Two or more other CVD risk factors are present in the adolescent patient

The minimum goal of treatment in pediatric and adolescent patients is to achieve a mean LDL-C <130 mg/dL. The optimal age at which to initiate lipid-lowering therapy to decrease the risk of symptomatic adulthood CAD has not been determined.

*General Recommendations*

Prior to initiating therapy with simvastatin, secondary causes for hypercholesterolemia (e.g., hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure total-C, HDL-C, and TG. For patients with TG less than 400 mg/dL (< 4.5 mmol/L), LDL-C can be estimated using the following equation:

$$\text{LDL-C} = \text{total-C} - [(0.20 \times \text{TG}) + \text{HDL-C}]$$

For TG levels > 400 mg/dL (> 4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In many hypertriglyceridemic patients, LDL-C may be low or normal despite elevated total-C. In such cases, ZOCOR is not indicated.

Lipid determinations should be performed at intervals of no less than four weeks and dosage adjusted according to the patient's response to therapy.

The NCEP Treatment Guidelines are summarized in Table 6:

TABLE 6
NCEP Treatment Guidelines:
LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

| Risk Category | LDL Goal (mg/dL) | LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL) | LDL Level at Which to Consider Drug Therapy (mg/dL) |
|---|---|---|---|
| CHD† or CHD risk equivalents (10-year risk >20%) | <100 | ≥100 | ≥130 (100-129: drug optional)‡ |
| 2+ Risk factors (10 year risk ≤20%) | <130 | ≥130 | 10-year risk 10-20%: ≥130<br>10-year risk <10%: ≥160 |
| 0-1 Risk factor§ | <160 | ≥160 | ≥190 (160-189: LDL-lowering drug optional) |

† CHD, coronary heart disease

‡ Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

§ Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dL, non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C is ≥ 130 mg/dL (see NCEP Treatment Guidelines, above).

The NCEP classification of cholesterol levels in pediatric patients with a familial history of either hypercholesterolemia or premature cardiovascular disease is summarized in Table 7.

TABLE 7
NCEP Classification of Cholesterol Levels in Pediatric Patients with a Familial History of Either HeFH or Premature CVD

| Category | Total-C (mg/dL) | LDL-C (mg/dL) |
|---|---|---|
| Acceptable | <170 | <110 |
| Borderline | 170-199 | 110-129 |
| High | ≥200 | ≥130 |

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the total-C be used to monitor therapy.

ZOCOR is indicated to reduce elevated LDL-C and TG levels in patients with Type IIb hyperlipidemia (where hypercholesterolemia is the major abnormality). However, it has not been studied in conditions where the major abnormality is elevation of chylomicrons (i.e., hyperlipidemia Fredrickson types I and V).[4]

## CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

*Pregnancy and lactation.* Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as ZOCOR to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, ZOCOR is contraindicated during pregnancy and in nursing mothers. **ZOCOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If the patient becomes pregnant while taking this drug, ZOCOR should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see PRECAUTIONS, *Pregnancy*).

## WARNINGS

***Myopathy/Rhabdomyolysis***

Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10X the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

- **The risk of myopathy/rhabdomyolysis is increased by concomitant use of simvastatin with the following:**

**Potent inhibitors of CYP3A4: Cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily), particularly with higher doses of simvastatin** (see below; CLINICAL PHARMACOLOGY, *Pharmacokinetics*; PRECAUTIONS, *Drug Interactions, CYP3A4 Interactions*).

**Lipid-lowering drugs that can cause myopathy when given alone: Gemfibrozil, other fibrates, or lipid-lowering doses (≥1 g/day) of niacin, particularly with higher doses of simvastatin** (see below; PRECAUTIONS, *Drug Interactions, Interactions with lipid-lowering drugs that can cause myopathy when given alone*).

**Other drugs: Amiodarone or verapamil with higher doses of simvastatin** (see PRECAUTIONS, *Drug Interactions, Other drug interactions*). In an ongoing clinical trial, myopathy has been reported in 6% of patients receiving simvastatin 80 mg and amiodarone. In an analysis of clinical trials involving 25,248 patients treated with simvastatin 20 to 80 mg, the incidence of myopathy was higher in patients receiving verapamil and simvastatin (4/635; 0.63%) than in patients taking simvastatin without a calcium channel blocker (13/21,224; 0.061%).

• **The risk of myopathy/rhabdomyolysis is dose related.** The incidence in clinical trials, in which patients were carefully monitored and some interacting drugs were excluded, has been approximately 0.02% at 20 mg, 0.07% at 40 mg and 0.3% at 80 mg.

**Consequently:**

**1. Use of simvastatin concomitantly with itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) should be avoided.** If treatment with itraconazole, ketoconazole, erythromycin, or clarithromycin is unavoidable, therapy with simvastatin should be suspended during the course of treatment. Concomitant use with other medicines labeled as having a potent inhibitory effect on CYP3A4 at therapeutic doses should be avoided unless the benefits of combined therapy outweigh the increased risk.

**2. The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with cyclosporine, gemfibrozil, other fibrates or lipid-lowering doses (≥1 g/day) of niacin. The combined use of simvastatin with fibrates or niacin should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination.** Addition of these drugs to simvastatin typically provides little additional reduction in LDL-C, but further reductions of TG and further increases in HDL-C may be obtained.

**3. The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone or verapamil. The combined use of simvastatin at doses higher than 20 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy.**

**4. All patients starting therapy with simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Simvastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected.** The presence of these symptoms, and/or a CK level >10 times the ULN indicates myopathy. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved. Periodic CK determinations may be considered in patients starting therapy with simvastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

**5.** Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. Therapy with simvastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

*Liver Dysfunction*

**Persistent increases (to more than 3X the ULN) in serum transaminases have occurred in approximately 1% of patients who received simvastatin in clinical studies.** When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

In 4S (see CLINICAL PHARMACOLOGY, *Clinical Studies*), the number of patients with more than one transaminase elevation to > 3X ULN, over the course of the study, was not significantly different between the simvastatin and placebo groups (14 [0.7%] vs. 12 [0.6%]). Elevated transaminases resulted in the discontinuation of 8 patients from therapy in the simvastatin group (n=2,221) and 5 in the placebo group (n=2,223). Of the 1,986 simvastatin treated patients in 4S with normal liver function tests (LFTs) at baseline, only 8 (0.4%) developed consecutive LFT elevations to > 3X ULN and/or were discontinued due to transaminase elevations during the 5.4 years (median follow-up) of the study. Among these 8 patients, 5 initially developed these abnormalities within the first year. All of the patients in this study received a starting dose of 20 mg of simvastatin; 37% were titrated to 40 mg.

In 2 controlled clinical studies in 1,105 patients, the 12-month incidence of persistent hepatic transaminase elevation without regard to drug relationship was 0.9% and 2.1% at the 40- and 80-mg

dose, respectively. No patients developed persistent liver function abnormalities following the initial 6 months of treatment at a given dose.

**It is recommended that liver function tests be performed before the initiation of treatment, and thereafter when clinically indicated. Patients titrated to the 80-mg dose should receive an additional test prior to titration, 3 months after titration to the 80-mg dose, and periodically thereafter (e.g., semiannually) for the first year of treatment.** Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3X ULN or greater persist, withdrawal of therapy with ZOCOR is recommended.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of simvastatin.

As with other lipid-lowering agents, moderate (less than 3X ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and did not require interruption of treatment.

## PRECAUTIONS

*General*

Simvastatin may cause elevation of CK and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with simvastatin.

***Information for Patients***

**Patients should be advised about substances they should not take concomitantly with simvastatin and be advised to report promptly unexplained muscle pain, tenderness, or weakness (see list below and WARNINGS, *Myopathy/Rhabdomyolysis*). Patients should also be advised to inform other physicians prescribing a new medication that they are taking ZOCOR.**

*Drug Interactions*

*CYP3A4 Interactions*

Simvastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of simvastatin.

**See WARNINGS, *Myopathy/Rhabdomyolysis*, and CLINICAL PHARMACOLOGY, *Pharmacokinetics*.**

**Itraconazole**
**Ketoconazole**
**Erythromycin**
**Clarithromycin**
**HIV protease inhibitors**
**Nefazodone**
**Cyclosporine**
**Large quantities of grapefruit juice (>1 quart daily)**

*Interactions with lipid-lowering drugs that can cause myopathy when given alone*

The risk of myopathy is also increased by the following lipid-lowering drugs that are not potent CYP3A4 inhibitors, but which can cause myopathy when given alone.

**See WARNINGS, *Myopathy/Rhabdomyolysis*.**
**Gemfibrozil**
**Other fibrates**
**Niacin (nicotinic acid) (≥1 g/day)**

*Other drug interactions*

*Amiodarone or Verapamil:* The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil (see WARNINGS, *Myopathy/Rhabdomyolysis*).

*Propranolol:* In healthy male volunteers there was a significant decrease in mean $C_{max}$, but no change in AUC, for simvastatin total and active inhibitors with concomitant administration of single doses of ZOCOR and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.

*Digoxin:* Concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 ng/mL) in digoxin concentrations in plasma (as measured by a radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when simvastatin is initiated.

*Warfarin:* In two clinical studies, one in normal volunteers and the other in hypercholesterolemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. With other reductase inhibitors, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

*CNS Toxicity*

Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the mean plasma drug level in humans taking 80 mg/day.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean plasma drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced mean plasma drug levels that were about 14 times higher than the mean plasma drug levels in humans taking 80 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

There were cataracts in female rats after two years of treatment with 50 and 100 mg/kg/day (22 and 25 times the human AUC at 80 mg/day, respectively) and in dogs after three months at 90 mg/kg/day (19 times) and at two years at 50 mg/kg/day (5 times).

*Carcinogenesis, Mutagenesis, Impairment of Fertility*

In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8 times higher than the mean human plasma drug level, respectively (as total inhibitory activity based on AUC) after an 80-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day.

In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed (mean plasma drug levels were 1 times higher than humans given 80 mg simvastatin as measured by AUC).

In a two-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC).

A second two-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms

appears to be consistent with findings from other HMG-CoA reductase inhibitors. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80 milligram daily dose.

No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day, (which produces exposure levels 22 times higher than those in humans taking 80 mg/day based on surface area, mg/m$^2$), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day, (approximately 2 times the human exposure, based on AUC, at 80 mg/day). The clinical significance of these findings is unclear.

*Pregnancy*

*Pregnancy Category X*

See CONTRAINDICATIONS.

Safety in pregnant women has not been established.

Simvastatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses up to 10 mg/kg daily. These doses resulted in 3 times (rat) or 3 times (rabbit) the human exposure based on mg/m$^2$ surface area. However, in studies with another structurally-related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice.

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review[5] of approximately 100 prospectively followed pregnancies in women exposed to ZOCOR or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3- to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with ZOCOR during pregnancy (see CONTRAINDICATIONS), treatment should be immediately discontinued as soon as pregnancy is recognized. ZOCOR should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

*Nursing Mothers*

It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants (see CONTRAINDICATIONS).

*Pediatric Use*

Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least 1 year post-menarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses greater than 40 mg have not been studied in this population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. See CLINICAL PHARMACOLOGY, *Clinical Studies in Adolescents;* ADVERSE REACTIONS, *Adolescent Patients*; and DOSAGE AND ADMINISTRATION, *Adolescents (10-17 years of age) with Heterozygous Familial Hypercholesterolemia*. Adolescent females should be counseled on appropriate contraceptive methods while on simvastatin therapy (see CONTRAINDICATIONS and PRECAUTIONS, *Pregnancy).* Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

[5] Manson, J.M., Freyssinges, C., Ducrocq, M.B., Stephenson, W.P., Postmarketing Surveillance of Lovastatin and Simvastatin Exposure During Pregnancy, *Reproductive Toxicology*, 10(6):439-446, 1996.

*Geriatric Use*

A pharmacokinetic study with simvastatin showed the mean plasma level of HMG-CoA reductase inhibitory activity to be approximately 45% higher in elderly patients between 70-78 years of age compared with patients between 18-30 years of age. In 4S, 1,021 (23%) of 4,444 patients were 65 or older. In 4S, lipid-lowering efficacy was at least as great in elderly patients compared with younger patients. In this study, ZOCOR significantly reduced total mortality and CHD mortality in elderly patients with a history of CHD. There were no overall differences in safety between older and younger patients in 4S. In HPS, 52% of patients were elderly (4,891 patients 65-69 years and 5,806 patients 70 years or older). The relative risk reductions of CHD death, non-fatal MI, coronary and non-coronary revascularization procedures, and stroke were similar in older and younger patients (see CLINICAL PHARMACOLOGY). In HPS, among 32,145 patients entering the active run-in period, there were 2 cases of myopathy/rhabdomyolysis; these patients were aged 67 and 73. Of the 7 cases of myopathy/rhabdomyolysis among 10,269 patients allocated to simvastatin, 4 were aged 65 or more (at baseline), of whom one was over 75.

## ADVERSE REACTIONS

In the pre-marketing controlled clinical studies and their open extensions (2,423 patients with mean duration of follow-up of approximately 18 months), 1.4% of patients were discontinued due to adverse experiences attributable to ZOCOR. Adverse reactions have usually been mild and transient. ZOCOR has been evaluated for serious adverse reactions in more than 21,000 patients and is generally well tolerated.

*Clinical Adverse Experiences*

*In Adults*

Adverse experiences occurring in adults at an incidence of 1% or greater in patients treated with ZOCOR, regardless of causality, in controlled clinical studies are shown in Table 8.

TABLE 8
Adverse Experiences in Clinical Studies
Incidence 1 Percent or Greater, Regardless of Causality

| | ZOCOR (N = 1,583) % | Placebo (N = 157) % | Cholestyramine (N = 179) % |
|---|---|---|---|
| *Body as a Whole* | | | |
| Abdominal pain | 3.2 | 3.2 | 8.9 |
| Asthenia | 1.6 | 2.5 | 1.1 |
| *Gastrointestinal* | | | |
| Constipation | 2.3 | 1.3 | 29.1 |
| Diarrhea | 1.9 | 2.5 | 7.8 |
| Dyspepsia | 1.1 | — | 4.5 |
| Flatulence | 1.9 | 1.3 | 14.5 |
| Nausea | 1.3 | 1.9 | 10.1 |
| *Nervous System/ Psychiatric* | | | |
| Headache | 3.5 | 5.1 | 4.5 |
| *Respiratory* | | | |
| Upper respiratory infection | 2.1 | 1.9 | 3.4 |

*Scandinavian Simvastatin Survival Study*

*Clinical Adverse Experiences*

In 4S (see CLINICAL PHARMACOLOGY, *Clinical Studies*) involving 4,444 patients treated with 20-40 mg/day of ZOCOR (n=2,221) or placebo (n=2,223), the safety and tolerability profiles were comparable between groups over the median 5.4 years of the study. The clinical adverse experiences reported as possibly, probably, or definitely drug-related in ≥ 0.5% in either treatment group are shown in Table 9.

TABLE 9
Drug-Related Clinical Adverse Experiences in 4S
Incidence 0.5 Percent or Greater

| | ZOCOR (N = 2,221) % | Placebo (N = 2,223) % |
|---|---|---|
| *Body as a Whole* | | |
| Abdominal pain | 0.9 | 0.9 |
| *Gastrointestinal* | | |
| Diarrhea | 0.5 | 0.3 |
| Dyspepsia | 0.6 | 0.5 |
| Flatulence | 0.9 | 0.7 |
| Nausea | 0.4 | 0.6 |
| *Musculoskeletal* | | |
| Myalgia | 1.2 | 1.3 |
| *Skin* | | |
| Eczema | 0.8 | 0.8 |
| Pruritus | 0.5 | 0.4 |
| Rash | 0.6 | 0.6 |
| *Special Senses* | | |
| Cataract | 0.5 | 0.8 |

*Heart Protection Study*
*Clinical Adverse Experiences*

In HPS (see CLINICAL PHARMACOLOGY, *Clinical Studies*), involving 20,536 patients treated with ZOCOR 40 mg/day (n=10,269) or placebo (n=10,267), the safety profiles were comparable between patients treated with ZOCOR and patients treated with placebo over the mean 5 years of the study. In this large trial, only serious adverse events and discontinuations due to any adverse events were recorded. Discontinuation rates due to adverse experiences were comparable (4.8% in patients treated with ZOCOR compared with 5.1% in patients treated with placebo). The incidence of myopathy/rhabdomyolysis was <0.1% in patients treated with ZOCOR.

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with simvastatin therapy.
*Skeletal:* muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.
*Neurological:* dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances, anxiety, insomnia, depression.
*Hypersensitivity Reactions:* An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.
*Gastrointestinal:* pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.
*Skin:* alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.
*Reproductive:* gynecomastia, loss of libido, erectile dysfunction.
*Eye:* progression of cataracts (lens opacities), ophthalmoplegia.
*Laboratory Abnormalities:* elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.
*Laboratory Tests*

Marked persistent increases of serum transaminases have been noted (see WARNINGS, *Liver Dysfunction*). About 5% of patients had elevations of CK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CK. Muscle pain or dysfunction usually was not reported (see WARNINGS, *Myopathy/Rhabdomyolysis*).
*Concomitant Lipid-Lowering Therapy*

In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine. The combined use of simvastatin at doses exceeding 10 mg/day with gemfibrozil, other fibrates or lipid-lowering doses (≥1 g/day) of niacin should be avoided (see WARNINGS, *Myopathy/Rhabdomyolysis*).

*Adolescent Patients (ages 10-17 years)*

In a 48-week controlled study in adolescent boys and girls who were at least 1 year post-menarche, 10-17 years of age with heterozygous familial hypercholesterolemia (n=175), the safety and tolerability profile of the group treated with ZOCOR (10-40 mg daily) was generally similar to that of the group treated with placebo, with the most common adverse experiences observed in both groups being upper respiratory infection, headache, abdominal pain, and nausea. (see CLINICAL PHARMACOLOGY, *Clinical Studies in Adolescents*, and PRECAUTIONS, *Pediatric Use*).

## OVERDOSAGE

Significant lethality was observed in mice after a single oral dose of 9 g/m$^2$. No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 g/m$^2$, respectively. No specific diagnostic signs were observed in rodents. At these doses the only signs seen in dogs were emesis and mucoid stools.

A few cases of overdosage with ZOCOR have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 450 mg. Until further experience is obtained, no specific treatment of overdosage with ZOCOR can be recommended.

The dialyzability of simvastatin and its metabolites in man is not known at present.

## DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet. In patients with CHD or at high risk of CHD, ZOCOR can be started simultaneously with diet. The dosage should be individualized according to the goals of therapy and the patient's response. (For the treatment of adult dyslipidemia, see NCEP Treatment Guidelines. For the reduction in risks of major coronary events, see CLINICAL PHARMACOLOGY, *Clinical Studies in Adults.*) The dosage range is 5-80 mg/day (see below).

The recommended usual starting dose is 20 to 40 mg once a day in the evening. For patients at high risk for a CHD event due to existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, the recommended starting dose is 40 mg/day. Lipid determinations should be performed after 4 weeks of therapy and periodically thereafter. See below for dosage recommendations in special populations (i.e., homozygous familial hypercholesterolemia, adolescents and renal insufficiency) or for patients receiving concomitant therapy (i.e., cyclosporine, amiodarone, verapamil, fibrates or niacin).

*Patients with Homozygous Familial Hypercholesterolemia*

The recommended dosage for patients with homozygous familial hypercholesterolemia is ZOCOR 40 mg/day in the evening or 80 mg/day in 3 divided doses of 20 mg, 20 mg, and an evening dose of 40 mg. ZOCOR should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

*Adolescents (10-17 years of age) with Heterozygous Familial Hypercholesterolemia*

The recommended usual starting dose is 10 mg once a day in the evening. The recommended dosing range is 10-40 mg/day; the maximum recommended dose is 40 mg/day. Doses should be individualized according to the recommended goal of therapy (see NCEP Pediatric Panel Guidelines[6] and CLINICAL PHARMACOLOGY). Adjustments should be made at intervals of 4 weeks or more.

*Concomitant Lipid-Lowering Therapy*

ZOCOR is effective alone or when used concomitantly with bile-acid sequestrants. If ZOCOR is used in combination with gemfibrozil, other fibrates or lipid-lowering doses (≥1 g/day) of niacin, the dose of ZOCOR should not exceed 10 mg/day (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*).

*Patients taking Cyclosporine*

In patients taking cyclosporine concomitantly with ZOCOR (see WARNINGS, *Myopathy/Rhabdomyolysis*), therapy should begin with 5 mg/day and should not exceed 10 mg/day.

*Patients taking Amiodarone or Verapamil*

In patients taking amiodarone or verapamil concomitantly with ZOCOR, the dose should not exceed 20 mg/day (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*, *Other drug interactions*).

[6] National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics*. 89(3):495-501. 1992.

*Patients with Renal Insufficiency*

Because ZOCOR does not undergo significant renal excretion, modification of dosage should not be necessary in patients with mild to moderate renal insufficiency. However, caution should be exercised when ZOCOR is administered to patients with severe renal insufficiency; such patients should be started at 5 mg/day and be closely monitored (see CLINICAL PHARMACOLOGY, *Pharmacokinetics* and WARNINGS, *Myopathy/Rhabdomyolysis*).

**HOW SUPPLIED**

No. 3588 — Tablets ZOCOR 5 mg are buff, shield-shaped, film-coated tablets, coded MSD 726 on one side and ZOCOR on the other. They are supplied as follows:

**NDC** 0006-0726-31 unit of use bottles of 30
**NDC** 0006-0726-61 unit of use bottles of 60
**NDC** 0006-0726-54 unit of use bottles of 90
**NDC** 0006-0726-28 unit dose packages of 100
**NDC** 0006-0726-82 bottles of 1000.

No. 3589 — Tablets ZOCOR 10 mg are peach, shield-shaped, film-coated tablets, coded MSD 735 on one side and ZOCOR on the other. They are supplied as follows:

**NDC** 0006-0735-31 unit of use bottles of 30
**NDC** 0006-0735-54 unit of use bottles of 90
**NDC** 0006-0735-28 unit dose packages of 100
**NDC** 0006-0735-82 bottles of 1000
**NDC** 0006-0735-87 bottles of 10,000.

No. 3590 — Tablets ZOCOR 20 mg are tan, shield-shaped, film-coated tablets, coded MSD 740 on one side and ZOCOR on the other. They are supplied as follows:

**NDC** 0006-0740-31 unit of use bottles of 30
**NDC** 0006-0740-61 unit of use bottles of 60
**NDC** 0006-0740-54 unit of use bottles of 90
**NDC** 0006-0740-28 unit dose packages of 100
**NDC** 0006-0740-82 bottles of 1000
**NDC** 0006-0740-87 bottles of 10,000.

No. 3591 — Tablets ZOCOR 40 mg are brick red, shield-shaped, film-coated tablets, coded MSD 749 on one side and ZOCOR on the other. They are supplied as follows:

**NDC** 0006-0749-31 unit of use bottles of 30
**NDC** 0006-0749-61 unit of use bottles of 60
**NDC** 0006-0749-54 unit of use bottles of 90
**NDC** 0006-0749-28 unit dose packages of 100
**NDC** 0006-0749-82 bottles of 1000.

No. 6577 — Tablets ZOCOR 80 mg are brick red, capsule-shaped, film-coated tablets, coded 543 on one side and 80 on the other. They are supplied as follows:

**NDC** 0006-0543-31 unit of use bottles of 30
**NDC** 0006-0543-61 unit of use bottles of 60
**NDC** 0006-0543-54 unit of use bottles of 90
**NDC** 0006-0543-28 unit dose packages of 100
**NDC** 0006-0543-82 bottles of 1000.

*Storage*

Store between 5-30°C (41-86°F).

---

Tablets ZOCOR (simvastatin) 5 mg, 10 mg, 20 mg, and 40 mg are manufactured by:

**MERCK & CO., INC.**
Whitehouse Station, NJ 08889, USA

Tablets ZOCOR (simvastatin) 80 mg are manufactured for:

**MERCK & CO., INC.**
Whitehouse Station, NJ 08889, USA

By:
MERCK SHARP & DOHME LTD,

ZOCOR® (simvastatin) ~~782544X~~

Cramlington, Northumberland, UK NE23 3JU

Issued ~~October 2002~~
Printed in USA

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 19-766/S-058

# MEDICAL REVIEW(s)

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: April 15, 2003

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 19-766/S-058
Zocor (simvastatin) tablets

SUBJECT: Brief note on labeling and clinical practice issues arising out of HPS

**HPS design and results**

The Heart Protection Study design and results are described in detail in the primary and secondary reviews of this sNDA. Briefly, HPS enrolled 20,536 patients with CHD or at risk because of DM, other vascular disease, or risk factors for CHD, and randomized them 1:1 to Zocor 40 mg or placebo. Average treatment and follow up was ~5 years, and the study examined, as its primary objective, the impact of treatment on death due to all causes, CHD death, and non-CHD death. Other endpoints included the panoply of clinical manifestations of atherosclerotic disease, including NFMI, revascularization, stroke.

The trial "won" on the primary and on multiple non-primary endpoints, considering outcomes in the ITT population. The protocol pre-specified two composite endpoints as follows: major coronary events (MCE) included CHD death and NFMI, and major vascular events (MVE) included MCE, stroke, and revascularization, coronary and otherwise, all as first events. The composites were, on the one hand, justified/rationalized based on common pathogenesis (all manifestations of same underlying disease) and, on the other, were developed for reasons of practical importance to add power to analyses of effects of treatment by numerous subgroups of interest. Thus, the magnitude of the treatment effects on the various individual endpoints varied from subgroup to subgroup (and statistical significance was not universally found). Of note, though, the results for the composite vascular disease endpoints were consistent across the subgroups by a number of baseline variables, including gender, age, presence or absence of diabetes, and baseline cholesterol levels. These results thus provide proof of principle of the benefits of cholesterol lowering with simvastatin (and probably other statins as well) across a broad population of patients at risk for cardiovascular events.

The safety profile of simvastatin in this study was consistent with what has been observed previously. Two patients developed rhabdomyolysis on simvastatin during the 6-week run-in period (in which all 32,145 eligible screenees received simvastatin), and 4 others developed rhadbodmyolysis on simvastatin during the controlled phase of the trial (out of 10,269 randomized to simvastatin).

**Labeling**
Substantial changes are being made to the labeling for simvastatin. These include, but are not limited to:

1. addition of a description of HPS and its results in Clinical Studies,
2. changes to Indications and Usage to reflect expected benefits (based on the statistically significant individual endpoint outcomes of HPS) in patients at high risk for coronary events, with or without pre-existing CHD, and
3. changes to Dosage and Administration to reflect the recommended starting dose of 40 mg in patients at high risk for CHD events.

Of note, though the description of the study results notes the consistency of the effects of simvastatin on the cardiovascular disease composites across subgroups by baseline variables, including the subgroup with LDL-C < 100 mg/dL,

**Summary**
In sum, the results of HPS demonstrate the efficacy of cholesterol lowering with simvastatin and probably other statins in patients with incipient coronary and other atherosclerotic disease to reduce the risk of atherosclerotic events, including MI's (fatal and non-fatal), stroke, and need for revascularization (coronary and otherwise). This study presents the most compelling data to date on the benefits of statin therapy across a host of at-risk patients, including diabetics, elderly, hypertensives, and across the range of baseline risk factors, including low LDL-C. This trial proves the principal that LDL-C lowering (with or without other effects of statins) is beneficial for patients with atherosclerotic disease (asymptomatic/incipient or symptomatic/manifest), even if elevated LDL-C is not present and traditional risk assessment identifies factors other than LDL-C as placing them at substantial risk for CVD. Importantly, however, the trial does not in any way direct a new method of use of statins that ignores baseline cholesterol, LDL-C goals, and that no longer requires monitoring of response to treatment as a guide to optimization of lipid-lowering therapy.

**Recommendation**
This application should be approved and labeling changes as agreed upon with the sponsor implemented.

**Medical**
**Safety**
**Efficacy**
**Labeling**
NDA # 19-766-S-058
Drug: Zocor (simvastatin)
Proposal: changes to labeling based on HPS
04/16/03

**Biopharmaceutics**
**Pharmacology/Toxicology**
**Chemistry/ Microbiology**
The chemistry, manufacturing, and controls are satisfactory and the application is approvable from the standpoint of ONDC, pending satisfactory response to certain deficiencies identified. These were conveyed to the sponsor on
The site inspections were all acceptable.
A categorical exclusion from the environmental assessment was claimed by the sponsor and accepted by the Agency.

**DSI/Data Integrity**

**Financial disclosure**
The financial disclosure information is in order. The sponsor has certified that no investigator received outcome payments, that no investigator disclosed a proprietary interest in the product or an equity interest in the company, and that no investigator was the recipient of significant payments of other sorts.

**OPDRA/nomenclature**

**Recommendation**

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/

David Orloff
4/16/03 02:46:36 PM
MEDICAL OFFICER

# MEDICAL OFFICER REVIEW

**Division of Metabolic and Endocrine Drug Products (HFD-510)**

| | |
|---|---|
| **Application #:** 19-766 | **Application Type:** sNDA |
| **Sponsor:** Merck | **Proprietary Name:** Zocor |
| **Investigator:** Multiple (Not named) | **USAN Name:** simvastatin |
| **Category:** lipid-altering | **Route of Administration:** oral |
| **Reviewer:** Mary H. Parks, MD | **Review Date:** April 9, 2003 |

**SUBMISSIONS REVIEWED IN THIS DOCUMENT**

| Document Date | CDER Stamp Date | Submission Type | Comments |
|---|---|---|---|
| NDA 19-766/S058 | | SE1 | |

**REVIEW SUMMARY:**

The Heart Protection Study (HPS) was a multicenter, placebo-controlled study in patients with established heart disease and patients without clinically evident heart disease but with risk factors that might increase the risk of a coronary event. Patients were treated with simvastatin 40 mg daily or placebo for 5 years. In this trial, simvastatin therapy reduced the risk of CHD mortality by 18%, nonfatal MIs by 38%, strokes by 25%, and the need for a coronary and non-coronary revascularization procedure by 30 and 16%, respectively.

Previous statin trials have enrolled patients with other non-lipid risk factors for heart disease; however, insufficient numbers of patients studied precluded any conclusion on the benefits of statin therapy in relevant subgroups. In contrast, HPS enrolled 5,082 women, 5,963 diabetics (~90% with Type 2), 10,697 elderly patients (≥ 65 years of age), 3,421 patients with LDL-C ≤ 100 mg/dL, and 8,457 treated hypertensive patients allowing for adequate subgroup analyses. Simvastatin therapy produced significant risk reductions on nonfatal clinical CV events such as myocardial infarction and revascularization procedures regardless of the presence or absence of CHD, gender, age, diabetes, and baseline cholesterol levels.

An important observation from HPS is that for patients with diabetes or non-coronary atherosclerosis conditions (e.g., peripheral arterial disease, carotid disease, or history of stroke) but without clinically evident coronary heart disease, simvastatin therapy resulted in a greater risk reduction than similar patients who have clinically manifested coronary disease (e.g., MI, angina). Although it is not entirely clear why patients with higher risks for CV events derived less benefit from simvastatin therapy in this trial, these findings support the recent changes to the NCEP Guidelines which have identified patients with diabetes, peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease as CHD-risk equivalents and that lipid-lowering goals should be identical to those of patients with established heart disease.

Overall, the results of HPS extend the clinical benefits of simvastatin to a broader patient population than previously studied.

**Recommended Regulatory:** Approval

## MEDICAL TEAM LEADER'S REVIEW OF EFFICACY SUPPLEMENT

| | |
|---|---|
| **NDA** | 19-766/S058 |
| **Sponsor** | Merck Research Laboratories |
| **Drug** | Zocor (simvastatin) |
| **Indication** | Reduce risk of CV events in patients with CHD or with high risk for CVD based on the results of the **Heart Protection Study** |
| **Date of Submission** | April 19, 2003 |
| **Action Goal Date** | |
| **Primary Reviewers** | William Lubas, MD, PhD (medical)<br>Joy Mele, MS (statistics) |

### INTRODUCTION

The Heart Protection Study (HPS) is one of six large, placebo-controlled clinical outcome trial demonstrating clinical benefits associated with the use of a statin. The other five studies and their key features are summarized in the following table:

**Table 1. Primary and Secondary Prevention Trials with HMG-coA Reductase Inhibitors Demonstrating Clinical Benefit**

| CLINICAL TRIAL AND PRIMARY ENDPOINT MEASURED | MEAN BASELINE LIPIDS (MG/DL) | STATIN EVENT RATE | PLACEBO EVENT RATE | RELATIVE RISK |
|---|---|---|---|---|
| Primary Prevention Trials | | | | |
| WOSCOPS (n=6,595)<br>NF-MI/fatal CHD | LDL-C 192<br>TC 272 | 174/3302<br>(5.3%) | 248/3293<br>(7.5%) | 0.69 |
| AFCAPS/TexCAPS (n=6,605)<br>NF-MI/fatal CHD/UAP | LDL-C 150<br>TC 221 | 116/3304<br>(3.5%) | 183/3301<br>(5.5%) | 0.63 |
| Secondary Prevention Trials | | | | |
| 4S (n=4,444)<br>Total Mortality | LDL-C 189<br>TC 260 | 182/2221<br>(8.2%) | 256/2223<br>(11.5%) | 0.70 |
| CARE (n=4,159)<br>NF-MI/fatal CHD | LDL-C 139<br>TC 209 | 212/2081<br>(10.2%) | 274/2078<br>(13.2%) | 0.76 |
| LIPID (n=9,014)<br>Total CHD Mortality | LDL-C 150<br>TC 219 | 287/4512<br>(6.4%) | 373/4502<br>(8.3%) | 0.76 |

HPS differed from these other clinical trials in that it was both a primary and secondary prevention study enrolling patients with established heart disease or who had non-coronary conditions that placed them at high risk of experiencing a cardiac event over the ensuing 5 years. These conditions included non-coronary occlusive disease, diabetes mellitus, and treated hypertension. The lipid entry criterion was a non-fasting total-C $\geq$ 135 mg/dL.

The trial involved a 2 x 2 factorial design assessing the effects of simvastatin and vitamins, alone and in combination, on CVD. This memo will present only the

simvastatin treatment effect as there was no evidence of an effect from vitamin therapy on the clinical endpoints measured in this trial.

**CLINICAL STUDY DESIGN**

A total of 63,603 patients were screened from 69 hospitals within the United Kingdom with 32,145 (50.5%) entering a run-in period. The run-in period consisted first of a 4-wk placebo administration phase followed by 6 weeks of simvastatin monotherapy. Patients meeting study eligibility (see list below) were assigned to treatment with either simvastatin (simva/pbo or simva/vitamin) or placebo (pbo or vitamin) using an algorithm that balanced treatment assignment based on 10 pre-specified characteristics: age, sex, total-C, DBP, CHD/MI, stroke/TIA, PVD, diabetes, smoking, and ethnic origin (see Appendix 1 of J. Mele's review).

20,536 patients were allocated to treatment with simvastatin (n=10,269) or placebo (n=10,267) for an average treatment duration of 5.3 years. The study population was primarily Caucasian (97%) with the mean age being 63.5 years. Slightly more than half of the cohort had pre-existing heart disease (65% had any history of CHD), 29% were diabetics (26% were Type 2), and 41% had treated hypertension.

Mean baseline lipid measures were: LDL-C 131 mg/dL (median 128.8; range 29.6-373.6); HDL 41 mg/dL; TC 226 mg/dL; and TG (median) 155 mg/dL. Approximately 17% of the cohort had a baseline LDL-C < 100 mg/dL (n=3,421).

**Entry Criteria**

- 40 to 80 yrs
- screening nonfasting TC ≥ 135 mg/dL
- at least one of the following:
  - MI (definite or probable)
  - angina (stable or unstable)
  - PTCA or CABG
  - TIA
  - ischemic stroke
  - carotid endarterectomy or angioplasty
  - other arterial bypass sugery
  - amputation for vascular diseases
  - other evidence of PVD (intermittent claudication)
  - diabetes
  - treated HTN in men > 65 yrs age

**EFFICACY FINDINGS**

The primary efficacy endpoints were total mortality, CHD mortality, and non-CHD mortality.

Secondary and tertiary endpoints included non-fatal MIs, stroke, coronary and non-coronary revascularization procedures, hospitalizations for angina, and peripheral macrovascular complications of diabetes. The sponsor also identified two composite endpoints of interest: major coronary events (MCE) and major vascular events (MVE). MCE was comprised of CHD mortality or nonfatal MIs and MVE was comprised of MCE, stroke, or coronary or noncoronary revascularization procedure.

All efficacy endpoints were analyzed as time-to-first event.

**Primary Efficacy Results**

Total Mortality

The simvastatin group experienced 1,328 (12.9%) deaths compared to 1,507 (14.7%) in the placebo group. Simvastatin therapy resulted in a 13% RR reduction in all-cause mortality that was significant at a p=0.0003.

CHD Mortality

The simvastatin group experienced 587 (5.7%) CHD deaths versus 707 (6.9%) in the placebo group. Simvastatin therapy resulted in a 18% RR reduction in CHD mortality that was significant at a p=0.0005.

Non-CHD Mortality

The incidence of death due to other causes (non-CHD) was 7.2% in the simvastatin group versus 7.8% in the placebo group. Cause-specific mortality is summarized in the following table.

**Table 2. Mortality (%) in HPS by Treatment Group**

| | SIMVASTATIN N=10,269 | PLACEBO N=10,267 |
|---|---|---|
| All-cause mortality | 1,328 (12.9%) | 1,507 (14.7%) |
| CHD mortality | 587 (5.7%) | 707 (6.9%) |
| Other vascular | 194 (1.9%) | 230 (2.2%) |
| Cancer | 359 (3.5%) | 345 (3.4%) |
| Respiratory | 90 (0.9%) | 114 (1.1%) |
| Other medical | 82 (0.8%) | 90 (0.9%) |
| Non-medical | 16 (0.2%) | 21 (0.2%) |

**Secondary/Tertiary Efficacy Results**

Major Coronary Events (MCE)

The incidence of experiencing either a CHD death or non-fatal MI as an initial event was 8.7% in the simvastatin group versus 11.8% in the placebo group. Simvastatin therapy resulted in a 27% RR reduction for MCE that was significant at p<0.0001. Table 3 summarizes the results of this composite endpoint.

**Table 3. Major Coronary Events (%) in HPS by Treatment Group**

| | SIMVASTATIN N=10,269 | PLACEBO N=10,267 |
|---|---|---|
| Major Coronary Events (MCE) | 898 (8.7%) | 1,212 (11.8%) |
| CHD mortality | 541 (5.3%) | 638 (6.2%) |
| Nonfatal MI | 357 (3.5%) | 574 (5.6%) |

The difference in the incidence of experiencing a nonfatal MI as the initial cardiac event between the two treatment groups was also significant with simvastatin therapy resulting in a 39% RR reduction (p<0.0001).

Major Vascular Events (MVE)

The incidence of experiencing either a CHD death, non-fatal MI, stroke, or revascularization procedure (coronary or non-coronary) as an initial event was 19.8% in the simvastatin group versus 25.2% in the placebo group. Simvastatin therapy resulted

in a 24% RR reduction for MVE that was significant at p<0.0001. Certain individual components of this composite endpoint were also evaluated by the FDA statisitican. Within the stroke category (ischemic and hemorrhagic), significant reductions were only observed for ischemic strokes. Simvastatin therapy reduced the risk for both coronary (CABG and PTCA) and non-coronary (peripheral, carotid, etc.) revascularization procedures. These findings are summarized in Table 4.

**Table 4. Stroke and Revascularization Procedures in HPS by Treatment Group (from FDA statistical review by Joy Mele, MS)**

| EVENT | SIMVASTATIN | PLACEBO | RR | 95% CI | P-VALUE |
|---|---|---|---|---|---|
| Total Stroke | 444 (4.3%) | 585 (5.7%) | 0.75 | 0.66, 0.85 | <0.0001 |
| hemorrhagic | 39 (0.38%) | 45 (0.44%) | 0.86 | 0.56, 1.32 | 0.49 |
| ischemic | 290 (2.8%) | 409 (4.0%) | 0.70 | 0.60, 0.81 | <0.0001 |
| Revascularization | 939 (9.1%) | 1205 (11.7%) | 0.76 | 0.70, 0.83 | <0.0001 |
| Coronary | 513 (5%) | 725 (7.1%) | 0.69 | 0.62, 0.78 | <0.0001 |
| Noncoronary | 450 (4.4%) | 532 (5.2%) | 0.84 | 0.74, 0.95 | 0.005 |

Hospitalizations for Angina

As a tertiary efficacy analysis, the sponsor also evaluated hospitalizations for angina. There was a significant reduction in the risk of being hospitalized for angina (RR 0.83, p<0.0001) based on 1,030 (10%) events occurring in the simvastatin group versus 1,224 (11.9%) occurring in the placebo group.

The primary medical reviewer, Dr. William Lubas, inquired about the adjudication procedures for this endpoint. Pre-defined objective criteria for identifying these patients were not established. Events were tallied based on review of discharge diagnoses from hospital medical records.

The clinical benefit of this tertiary efficacy finding was questionnable as the angina index score showed no difference between the two treatment groups.

Peripheral Macrovascular Complications of Diabetes

The sponsor analyzed the incidence of peripheral macrovascular complications in diabetics. The events consisted of peripheral revascularization procedures, lower limb amputations, and development of leg ulcers with revascularization procedures predominating in this composite measure (Table 5). The overall incidence was higher in the placebo group (6.5%) than the simvastatin group (5.2%) with a 21% relative risk reduction (p=0.03).

**Table 5. Peripheral Macrovascular Complications in Diabetics by Treatment Group**

| | SIMVASTATIN N=2,978 | PLACEBO N=2,985 |
|---|---|---|
| Peripheral revascularization | 81 (2.7%) | 109 (3.7%) |
| Lower limb amputation | 41 (1.4%) | 48 (1.6%) |
| Leg ulcer | 34 (1.1%) | 37 (1.2%) |

Subgroup Analyses

The Heart Protection Study enrolled a large number of patients with efforts established to over-sample for elderly patients, females, and patients without CHD. Furthermore, qualifying risk factors for study entry resulted in the enrollment of a large number of patients with diabetes and hypertension. Risk reductions for mortality, nonfatal MI, stroke and revascularization procedures observed in selected subgroups are summarized in Table 6. The FDA statistical reviewer has summarized relative risks by these subgroups and other subgroups for all efficacy endpoints evaluated in her review.

**Table 6. Relative Risks* (95% CI) Among Specific Subgroups in HPS**

| | TTL MORTALITY | CHD MORTALITY | NF MI | STROKE | REVASC |
|---|---|---|---|---|---|
| Gender | | | | | |
| Male | 0.88 (0.81, 0.95) | 0.85 (0.75, 0.95) | 0.61 (0.53, 0.70) | 0.72 (0.62, 0.83) | 0.74 (0.68, 0.81) |
| Female | *0.86 (0.72, 1.02)* | 0.71 (0.53, 0.94) | 0.63 (0.45, 0.87) | *0.85 (0.66, 1.09)* | *0.88 (0.71, 1.1)* |
| Age- tertiles | | | | | |
| <60 | *0.91 (0.74, 1.12)* | *0.89 (0.67, 1.18)* | 0.53 (0.41, 0.69) | *0.80 (0.60, 1.07)* | 0.73 (0.64, 0.85) |
| 60-68 | 0.83 (0.73, 0.94) | 0.77 (0.64, 0.92) | 0.52 (0.42, 0.65) | 0.81 (0.66, 0.98) | 0.76 (0.66, 0.87) |
| >68 | 0.89 (0.80, 0.98) | 0.84 (0.72, 0.99) | 0.78 (0.63, 0.96) | 0.68 (0.57, 0.82) | 0.81 (0.69, 0.95) |
| Prior MI | 0.89 (0.80, 0.99) | 0.87 (0.75, 0.99) | 0.65 (0.54, 0.77) | 0.74 (0.61, 0.91) | 0.74 (0.65, 0.83) |
| Other CHD | 0.84 (0.71, 0.996) | 0.74 (0.57, 0.95) | 0.67 (0.51, 0.90) | *0.78 (0.60, 1.01)* | 0.78 (0.66, 0.92) |
| No CHD | 0.87 (0.76, 0.99) | 0.78 (0.62, 0.995) | 0.49 (0.37, 0.65) | 0.74 (0.61, 0.90) | 0.79 (0.68, 0.93) |
| Diabetes | 0.85 (0.74, 0.97) | 0.80 (0.66, 0.96) | 0.63 (0.49, 0.80) | 0.76 (0.61, 0.94) | 0.83 (0.70, 0.97) |
| with CHD | *0.92 (0.76, 1.1)* | *0.84 (0.66, 1.06)* | *0.75 (0.54, 1.05)* | *0.86 (0.62, 1.19)* | *0.90 (0.71, 1.12)* |
| without CHD | 0.79 (0.65, 0.97) | *0.77 (0.57, 1.04)* | 0.52 (0.36, 0.75) | 0.69 (0.52, 0.92) | 0.77 (0.61, 0.98) |
| No Diabetes | 0.88 (0.81, 0.96) | 0.84 (0.73, 0.96) | 0.60 (0.52, 0.71) | 0.74 (0.64, 0.86) | 0.74 (0.67, 0.82) |
| Hypertension | | | | | |
| Yes | 0.80 (0.71, 0.89) | 0.78 (0.67, 0.92) | 0.73 (0.60, 0.89) | 0.80 (0.67, 0.96) | 0.71 (0.62, 0.80) |
| No | *0.94 (0.85, 1.04)* | *0.86 (0.74, 1.01)* | 0.52 (0.43, 0.63) | 0.70 (0.59, 0.83) | 0.81 (0.73, 0.91) |

*relative risks is the incidence of event of interest in the simvastatin group divided by the incidence in placebo group.

Overall, risk reductions associated with simvastatin therapy were observed for all the endpoints measured across the subgroups analyzed although some did not reach statistical significance (*italicized in Table 6*) or were only marginally significant (upper bound of the 95% CI nearing 1.0). Interestingly, diabetics without established heart disease appeared to have greater risk reductions for cardiovascular events than diabetics with established heart disease. Similarly, greater risk reductions were observed in patients with peripheral vessel disease or cerebrovascular disease subgroups without a history heart disease compared to their counterpart with CHD (see J. Mele's review).

Both the FDA statistician and the sponsor analyzed the effect of treatment on numerous endpoints within the following subgroups: baseline LDL-C < 100 mg/dL; 100-130 mg/dL; and ≥ 130 mg/dL. The following table summarizes the relative risks (95% CI) by individual clinical events and by the two composite measures, MCE and MVE. Please

see Joy Mele's review for detailed tables with sample sizes and event rates by treatment group.

**Table 7. Relative Risks* (95% CI) by Screening LDL-C Levels**

| BASELINE LDL (MG/DL) | TOTAL MORTALITY | CHD DEATH | NF MI | STROKE | REVASC | MCE | MVE |
|---|---|---|---|---|---|---|---|
| < 100 | 0.92 (0.77, 1.1) | 0.96 (0.73, 1.3) | 0.51 (0.35, 0.75) | 0.74 (0.54, 1.01) | 0.78 (0.61, 0.99) | 0.76 (0.60, 0.95) | 0.76 (0.65, 0.89) |
| 100-130 | 0.82 (0.73, 0.93) | 0.71 (0.59, 0.86) | 0.57 (0.46, 0.72) | 0.70 (0.57, 0.87) | 0.77 (0.66, 0.90) | 0.65 (0.56, 0.75) | 0.74 (0.67, 0.81) |
| ≥ 130 | 0.89 (0.81, 0.99) | 0.86 (0.74, 1.01) | 0.66 (0.55, 0.79) | 0.79 (0.66, 0.94) | 0.76 (0.67, 0.85) | 0.77 (0.69, 0.87) | 0.78 (0.72, 0.84) |

*relative risks is the incidence of event of interest in the simvastatin group divided by the incidence in placebo group.

Significant risk reductions were observed for non-fatal MIs and the composite endpoints, MCE and MVE, across all three LDL-C subgroups. For patients with baseline LDL-C < 100 mg/dL, marginally significant risk reductions were observed for total strokes (p=0.054) and revascularization procedures (p=0.04). The risk reductions associated with simvastatin therapy for patients with baseline LDL< 100 mg/dL did not reach statistical significance for total mortality or CHD mortality.

## SAFETY FINDINGS

### Deaths and Serious AEs

Deaths in HPS were part of the primary endpoint and have been discussed in detail in the efficacy portion of this review (see Table 2 for incidence of cause-specific mortality). The incidence of cancer-related deaths was slightly higher in the simvastatin group (3.5%) versus the placebo group (3.4%); however, Dr. Lubas discussed cancer-related AEs in his review and found no statistically significant difference between simvastatin and placebo in the incidence of cancer at any individual site.

The incidence of serious AEs reported in HPS was similar between the two treatment groups [simvastatin (63%) vs. placebo (66%)].

### CK Elevations and AEs Related to Muscle Toxicity

The incidence of CK elevations > 5x and 10x ULN was higher in the simvastatin group (0.18% and 0.05%, respectively) compared to placebo (0.10% and 0.03%, respectively). From the sponsor's analysis, nine patients (0.09%) in the simvastatin group experienced myopathy (defined as CK > 10xULN) compared to 3 (0.03%) in the placebo group. Four (0.04%) simvastatin-treated patients experienced rhabdomyolysis (CK > 10,000 IU) versus 1 (0.01%) in the placebo group.

Dr. Lubas identified rhabdomyolysis cases in patients with CK > 10,000 and/or CK elevations associated with hospitalization for myopathy. Using this definition he noted a slightly higher incidence of rhabdomyolysis (n=6; 0.06%) in the simvastatin group compared to placebo (0.01%). He also discussed the use of concomitant medications which might increase the risk of muscle toxicity and found that 4 patients were on such medications (2 on erythromycin and 2 on verapamil). In addition, two patients receiving simvastatin during the active run-in period developed rhabdomyolysis and are not included in the aforementioned incidence rates. A 67-year old male had a CK level of

96,000 IU and a 73-year old male had a CK level reported as > 2500 IU with development of renal failure. Neither of these patients were allocated to treatment in the double-blind treatment phase of HPS.

Overall, regardless of definition used, the incidences of CK elevations and myopathy/rhabdomyolysis were higher in the simvastatin group than placebo although the rate remained low at < 0.1%. The safety results of HPS reflect what is currently discussed in the label on risk of myopathy.

There were too few cases of myopathy/rhabdomyolysis to determine if there is an increased risk in patients with lower baseline LDL-C levels.

**Elevations in Transaminase Levels**

The incidences of ALT elevations > 3x, > 6x, > 9x on single and multiple occasions were always higher in the simvastatin group compared to placebo; however, the overall rates of ALT elevations in the simvastatin group were low. The incidence of hepatitis or liver failure was identical between the two treatment groups (simvastatin; 0.2% versus placebo; 0.2%)

**Table 8. ALT Elevations in HPS; n(%)**

| ALT ELEVATION | SIMVASTATIN | PLACEBO |
|---|---|---|
| Single elevation | | |
| 3x ULN | 78 (0.78%) | 71 (0.71%) |
| 6x ULN | 16 (0.16%) | 15 (0.15%) |
| 9x ULN | 7 (0.07%) | 6 (0.06%) |
| Multiple elevations | | |
| 3x ULN | 24 (0.24%) | 13 (0.13%) |
| 6x ULN | 4 (0.04%) | 2 (0.02%) |
| 9x ULN | 3 (0.03%) | 1 (0.01%) |

Dr. Lubas also evaluated ALT elevations > 3xULN as a function of days in study and found that elevations continued throughout the entire length of the trial for both treatment groups and that there was no timepoint in which LFT monitoring was predictive of clinical disease.

Overall, although the incidences of ALT elevations were higher in the simvastatin group compared to placebo, these rates remained low with no difference in incidence of clinical liver disease between the simvastatin and placebo groups.

**LABELING**

**Proposed Labeling and Comments**

Significant changes were proposed to 3 sections of the label: CLINICAL PHARMACOLOGY, Clinical studies describing the conduct and results of HPS; INDICATIONS and USAGE; and DOSAGE and ADMINISTRATION. In addition, several changes were made to the WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS section of the label. Four teleconferences were held between the division and sponsor to negotiate the final approved label based on the review of this application. This section only highly certain relevant negotiation points in the label (please see final approved label attached with action letter).

Under CLINICAL PHARMACOLOGY
The attempt here was to describe the study population, conduct of the study, and results of the trial such that it is clear in whom simvastatin therapy will provide clinical benefit and what the expected benefits are. This trial enrolled a large number of diabetic (primarily Type 2) and elderly patients and benefits of treatment could be demonstrated across several different subgroups.

Key areas of negotiations also included a thorough discussion of the composite endpoints, major coronary and vascular events (MCE and MVE) and benefits observed in these endpoints regardless of baseline LDL-C levels. These data were summarized as text followed by a figure summarizing the risk ratios for MCE and MVE by relevant subgroups.

Under INDICATIONS and USAGE
The labeling under this section described the targeted population and the expected benefits. The following is the agreed-upon language specific to the HPS results for this section of the label.

Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

In patients with CHD or at high risk of CHD, ZOCOR can be started simultaneously with diet.

*Reductions in Risk of CHD Mortality and Cardiovascular Events*

In patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, ZOCOR is indicated to:

- Reduce the risk of total mortality by reducing CHD deaths.
- Reduce the risk of non-fatal myocardial infarction and stroke.
- Reduce the need for coronary and non-coronary revascularization procedures.

Under WARNINGS
The sponsor proposed to replace the recommendation for periodic post-baseline monitoring of LFTs with monitoring based on clinically symptomatology. Based on Dr. Lubas's review of the incidence of ALT elevations this proposal is acceptable for simvastatin doses below 80 mg. Patients treated with 80 mg should still have LFT monitoring periodically within the first year of therapy.

Under DOSAGE and ADMINISTRATION
The labeling under this section should describe how the results of HPS have changed the dosing instructions for simvastatin and should not reiterate the INDICATIONS and USAGE section. The Heart Protection Study initiated drug treatment with simvastatin 40 mg in eligible patients. Eligibility was based on clinical risk factors such as established heart disease, diabetes, PVD, and CVD. The following changes to the DOSAGE and ADMINISTRATION section were made based on the HPS results.

The patient should be placed on a standard cholesterol-lowering diet. In patients with CHD or at high risk of CHD, ZOCOR can be started simultaneously with diet. The dosage should be individualized according to the goals of therapy and the patient's response (For the treatment of adult dyslipidemia, see NCEP Treatment Guidelines. For

the reduction in risks of major coronary events, see CLINICAL PHARMACOLOGY, *Clinical Studies in Adults*). The dosage range is 5-80 mg/day (see below).

The recommended usual starting dose is 20 to 40 mg once a day in the evening. For patients at high risk for a CHD event due to existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, the recommended starting dose is 40 mg/day. Lipid determinations should be performed after 4 weeks of therapy and periodically thereafter. See below for dosage recommendations in special populations (i.e., homozygous familial hypercholesterolemia, adolescents and renal insufficiency) or for patients receiving concomitant therapy (i.e., cyclosporine, amiodarone, verapamil, fibrates or niacin).

**REGULATORY/ADMINISTRATIVE ISSUES**

Financial disclosure information was reviewed by Dr. Lubas and there was no evidence that financial interests of investigators and co-investigators influenced the results of this trial.

**CONCLUSIONS**

The Heart Protection Study (HPS) was a multicenter, placebo-controlled study in patients with established heart disease and patients without clinically evident heart disease but with risk factors that might increase the risk of a coronary event. Patients were treated with simvastatin 40 mg daily or placebo for 5 years. In this trial, simvastatin therapy reduced the risk of CHD mortality by 18%, nonfatal MIs by 38%, strokes by 25%, and the need for a coronary and non-coronary revascularization procedure by 30 and 16%, respectively.

Previous statin trials have enrolled patients with other non-lipid risk factors for heart disease; however, insufficient numbers of patients studied precluded any conclusion on the benefits of statin therapy in relevant subgroups. In contrast, HPS enrolled 5,082 women, 5,963 diabetics (~90% with Type 2), 10,697 elderly patients (≥ 65 years of age), 3,421 patients with LDL-C ≤ 100 mg/dL, and 8,457 treated hypertensive patients allowing for adequate subgroup analyses. Simvastatin therapy produced significant risk reductions on nonfatal clinical CV events such as myocardial infarction and revascularization procedures regardless of the presence or absence of CHD, gender, age, diabetes, and baseline cholesterol levels.

An important observation from HPS is that for patients with diabetes or non-coronary atherosclerosis conditions (e.g., peripheral arterial disease, carotid disease, or history of stroke) but <u>without</u> clinically evident coronary heart disease, simvastatin therapy resulted in a greater risk reduction than similar patients who have clinically manifested coronary disease (e.g., MI, angina). Although it is not entirely clear why patients with higher risks for CV events derived less benefit from simvastatin therapy in this trial, these findings support the recent changes to the NCEP Guidelines which have identified patients with diabetes, peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease as CHD-risk equivalents and that lipid-lowering goals should be identical to those of patients with established heart disease.

Overall, the results of HPS extend the clinical benefits of simvastatin to a broader patient population than previously studied.

**RECOMMENDATION**

This efficacy supplement should be approved.

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/s/

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Mary Parks
4/14/03 08:46:28 AM
MEDICAL OFFICER

David Orloff
4/14/03 06:28:05 PM
MEDICAL OFFICER
Concur. Approval.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 19-766/S-058

# STATISTICAL REVIEW(S)

# JOINT CLINICAL AND STATISTICAL REVIEW

NDA #: 19-766/Supplement 058

Drug: ZOCOR (simvastatin) tablets

Applicant: Merck Research Laboratories

Indication: Prevention of coronary heart disease based on the Heart Protection Study

Date of Submission: June 18, 2002

Documents Reviewed: Paper (2 volumes) and electronic volumes (\\CDSESUB1\N19766\S_058)

Medical Reviewer: William Lubas, M.D., Ph.D. (HFD-510)

Medical Division: Division of Metabolic and Endocrine Drug Products

Statistical Reviewer: Joy Mele, M.S. (HFD-715)

Statistical Division: Division of Biometrics 2

## *Table of Contents*

# Joint Clinical and Statistical Review sNDA 19-766 S_058

## Executive Summary

### I. Recommendations

**A. Recommendation on Approvability**

Approvable with revised labeling agreed to by applicant.

**B. Recommendation on Phase 4 Studies and/or Risk Management Steps**

None.

### II. Summary of Clinical Findings

The Heart Protection Study (HPS) was a multicenter, large, placebo-controlled trial designed to study the effects of simvastatin and antioxidant vitamins in patients at high risk of coronary heart disease (CHD) within five years of study entry. Patients had one or more of the following entry criteria:

- CHD (65%)
  - stable or unstable angina (53%)
  - myocardial infarction (MI, 41%)
  - coronary artery bypass graft (CABG, 16%)
  - percutaneous transluminal coronary angioplasty (PTCA, 7%)
- cerebrovascular disease (16%) [ transient ischemic attack (TIA) , stroke, carotid artery stenosis, and carotid endarterectomy]
- peripheral vascular disease (33%) [leg artery stenosis, leg surgery or intermittent claudication]
- diabetes (29%) [type 2 (26%) and type 1 (3%)]
- treated hypertension in males over 65 years of age (6%)

After screening, 32,145 patients entered a run-in period of four weeks of placebo and six weeks of simvastatin treatment. About 36% of the study population dropped out during the run-in for multiple reasons (the most common reason was patient wishes). A total of 20,536 patients were allocated to treatment with simvastatin (40 mg) and/or antioxidant vitamins (Vit. E 600 mg, Vit. C 250 mg, and beta-carotene 20 mg) in a 2 x 2 factorial study design. To achieve treatment group balance, patients were allocated using a covariate adaptive method which took into account the distribution of 10 baseline characteristics for patients already enrolled and minimized the

imbalance of those characteristics across the groups. Hence patients were not randomized to treatment in this trial. The mean duration of follow-up was 5.3 years.

Lipid profile measurements were performed at screening and at the end of the run-in for all patients. On-study measurements were performed yearly on random samples from 1,000 patients for the duration of the trial, and at the end of the trial for the patients still on study. About 80% of the patients had at least one LDL-C measurement during the double-blind treatment period. Measurements were performed in patients in the fed state which leads to an overestimation of TG levels. A direct LDL-C assay was used which leads to a slight underestimation in LDL-C levels compared to analyses using the Friedwald equation. Mean LDL-C at screening was 131 mg/dL in both groups. About 17% of the patients had a screening LDL-C<100 mg/dL. Note that for all analyses by screening LDL, one must assume the placebo patients return to their screening level after the run-in; there was not sufficient data to actually confirm this.

The treatment groups were well-balanced for baseline characteristics. About 25% of the patients were women and 97% were Caucasian. The mean and median age for patients was 64 years (range of 39 to 81) and about 6% were 75 years or older.

HPS showed that simvastatin 40 mg/day significantly reduced total and CHD mortality, non-fatal myocardial infarction (NFMI), stroke, revascularization procedures and events for two composite endpoints: major coronary events (MCE) comprised of CHD mortality and NFMI; and major vascular events (MVE) comprised of MCE, stroke and revascularization procedures (results are summarized below).

| Summary of HPS Results[1] | | | | |
|---|---|---|---|---|
| | **ZOCOR N=10,269 N (%)** | **Placebo N=10,267 N (%)** | **% Relative Risk Reduction** | **P Value** |
| **Primary Endpoints** | | | | |
| Total mortality | 1328 (12.9%) | 1507 (14.7%) | 13 | 0.0003 |
| CHD mortality | 587 (5.7%) | 707 (6.9%) | 18 | 0.0005 |
| **Secondary Endpoints** | | | | |
| MVE | 2033 (19.8%) | 2585 (25.2%) | 24 | <0.0001 |
| MCE | 898 (8.7%) | 1212 (11.8%) | 27 | <0.0001 |
| Non-fatal MI | 357 (3.5%) | 574 (5.6%) | [illegible] | <0.0001 |
| Stroke | 444 (4.3%) | 585 (5.7%) | 25 | <0.0001 |
| **Tertiary Endpoints** | | | | |
| Coronary revascularization | 513 (5.0%) | 725 (7.1%) | [illegible] | <0.0001 |
| Non-coronary revascularization | 450 (4.4%) | 532 (5.2%) | 16 | 0.006 |

[1] Results presented here were computed by FDA and agreed with the applicant's results with two exceptions; the applicant reported a RRR of 38 for non-fatal MI and 30 for coronary revascularization. Results for some subgroups mentioned in the text were only computed by FDA.

One of the objectives of this trial was to assess treatment effects in a number of subgroups including prior qualifying disease (see Appendix 1 for a complete listing of subgroups). In most subgroups, statistically significant treatment effects were observed with relative risk reductions consistent with the effect observed for all patients.

Statistically significant reductions in events for patients on simvastatin compared to placebo, for all endpoints, were seen regardless of prior qualifying disease (MI, other CHD, non-CHD, diabetes, or hypertension). However, results for diabetics with CHD, a high risk group of about 2,000 patients, consistently showed smaller relative risk reductions (16% for CHD mortality, 19% for MCE, 14% for MVE, and 14% for stroke) and non-significant results ($p>0.09$ for mortality endpoints and NFMI) or borderline significant results ($p=0.04$ for MCE, MVE and stroke) in contrast to the diabetic subgroup without CHD where statistically significant results were seen for all endpoints. Diabetics without CHD had about double the relative risk reductions (23% for CHD mortality, 36% for MCE, 28% for MVE, and 31% for stroke), seen for diabetics with CHD.

The event rates for women were consistently lower than for men and, consequently, risk reductions tended to be less significant; non-significant results were observed for women for total mortality ($p=0.09$) and for stroke ($p=0.19$).

An inadequate number of Africans, Orientals and Hispanics were enrolled in this trial to make any efficacy or safety claims for these populations.

Patients 65 years of age and older showed significant reductions in risk for all endpoints. Patients under 65 years of age failed to show benefit from simvastatin treatment for mortality endpoints (both total and CHD) and stroke where their event rates were low; however, benefit was observed on all other non-fatal endpoints and on the composite endpoints.

Results for subgroups defined by LDL-C level at screening generally showed statistically significant risk reductions due to simvastatin treatment, though the results in patients with LDL-C<100mg/dL tended to show smaller and less significant risk reductions than for patients with LDL-C≥100mg/dL. Further examination of the LDL-C<100mg/dL group by FDA showed that patients with high HDL-C (≥39mg/dL, median) did not show a benefit on MCE (relative risk reduction of 5%, $p=0.77$) but did show borderline significant results on MVE ($p=0.05$) primarily due to a risk reduction in stroke. These results clearly contrast with results of a similarly sized group (n=1575) with low HDL-C (<39/mg/dL, median) where the MCE rate was 13.3% and the relative risk reduction was 36% ($p=0.004$).

Non-serious adverse events were not captured in this trial. With respect to serious adverse events, there was a greater incidence in musculoskeletal adverse events, including CK elevations >10xULN, discontinuations for muscle enzyme elevations, and rhabdomyolysis/serious myopathy on simvastatin compared to placebo, but these rates were quite low (<0.1%). There was one possible case of drug-related liver failure and more patients experienced multiple ALT elevations >3xULN in the simvastatin group compared to placebo, but the incidence was quite

low (<0.3%). There was no evidence that frequent liver function monitoring without clinical evidence of liver disease was helpful in preventing serious drug-related liver disease. There was no clear association between neurological adverse events or cancer and the chronic use of simvastatin in this trial.

Patients with elevations in CK, liver function tests and serum creatinine above predetermined baseline levels were excluded from the study. In addition a large percentage of the patients (36%) withdrew from the study after the active run-in period. Therefore, it is possible that patients who were more likely to have certain serious adverse events on simvastatin could have been selected out prior to treatment allocation and the low incidence of adverse events observed in this study may not be representative of actual use in the general population.

In conclusion, the clinical information provided from HPS supports the safety and efficacy of Zocor 40mg/day for the treatment of patients at high risk of coronary events because of existing CHD, diabetes, peripheral vascular disease, history of stroke or other cerebrovascular disease to reduce the risk of total mortality by reducing CHD deaths, to reduce the risk of NFMI and stroke, and to reduce the need for coronary and non-coronary revascularization procedures. Whereas the benefits of Zocor 40mg/day were evident in patients in all subgroups with respect to baseline LDL-C, it is still important for patients on chronic therapy with Zocor to have periodic lipid determinations to assess the need for dose adjustment and /or other lipid lowering therapies.

## *Joint Clinical and Statistical Review*

## I. Introduction and Background

### A. Drug Established and Proposed Trade Name, Drug Class, Applicant's Proposed Indication(s), Dose, Regimens, Age Groups

Simvastatin (Zocor™) is a member of the statin class of lipid lowering compounds, which inhibit HMG-CoA reductase and reduce cholesterol synthesis. The dosage range is 5 to 80mg/day. It is currently approved for patients with:

HYPERLIPIDEMIA

- to reduce elevated total-C, LDL-C, Apo B, and TG, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson types IIa and IIb);
- for the treatment of patients with hypertriglyceridemia (Fredrickson type IV hyperlipidemia);
- for the treatment of patients with primary dysbetalipoproteinemia (Fredrickson type III hyperlipidemia);
- to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL-C apheresis) or if such treatments are unavailable.

(CORONARY HEART DISEASE)

In patients with coronary heart disease and hypercholesterolemia, ZOCOR is indicated to:

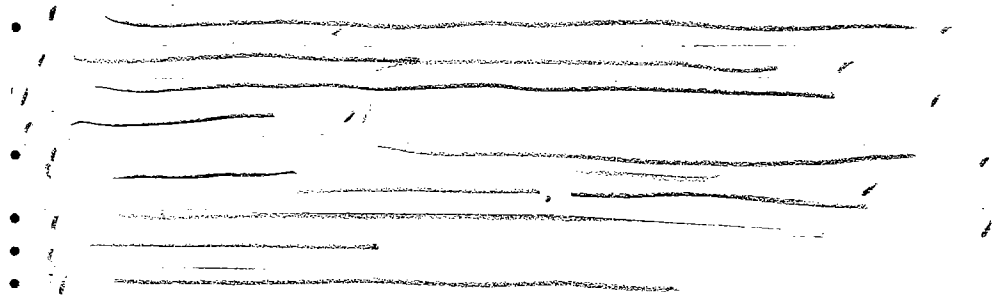
- Reduce the risk of total mortality by reducing coronary death;
- Reduce the risk of non-fatal myocardial infarction;
- Reduce the risk for undergoing myocardial revascularization procedures;
- Reduce the risk of stroke or transient ischemic attack.

The applicant has submitted data from HPS to support reductions in risk of CHD mortality and cardiovascular events in patients at high risk of coronary events because of existing CHD, diabetes, peripheral vascular disease, history of stroke or other cerebrovascular disease regardless of baseline LDL-C. The applicant seeks the following indications:

REDUCTION in RISK of CHD MORTALITY and CARDIOVASCULAR EVENTS

Zocor is indicated to:

- Reduce the risk of total mortality by reducing CHD deaths;



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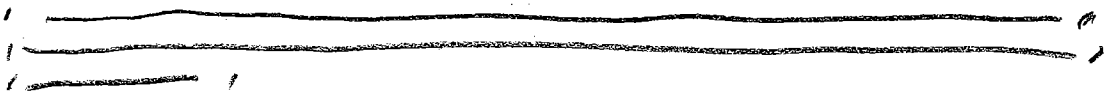


## II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

N/A

## III. Human Pharmacokinetics and Pharmacodynamics

N/A

## IV. Description of Clinical Data and Sources

### A. Overall Data

The data were submitted electronically in the following submissions:

6/18/02 Original submission, includes original data sets, labeling, case report forms, patient info, pediatric waiver info, financial disclosure, summary of study 102 (HPS)

9/16/02 Response to medical officer's questions about discrepancies in myopathy and rhabdomyolysis data between submission and Lancet publication

9/23/02 Compressed datasets updated to June 21, 2002; similar to data used in the Lancet publication

11/22/02 Response to medical officer's questions about datasets on non-randomized patients

1/31/03 Updated labeling

2/3/03 Response to statistician's request about details of minimization procedure

4/10/03 Response to medical officer's questions relating to safety review and financial disclosure

4/10/03A Updated EPDISCON.xpt file

4/10/03B Updates proposed labeling

### B. Tables Listing the Clinical Trials

All data were from clinical protocol 102 (HPS).

## V. Clinical Review Methods

### A. How the Review was Conducted

This was a joint clinical-statistical review. The medical reviewer, William Lubas M.D.-Ph.D., reviewed the safety data and wrote the safety section whereas the statistical reviewer, Joy Mele MS., reviewed the efficacy data and wrote the efficacy section. Other sections of the review were written primarily by the medical reviewer. The executive summary was written by both reviewers. The reviewers consulted with each other on many issues and so this document should be considered a collaborative effort.

All results (including tables and figures) presented in the efficacy part of this review were produced by the FDA statistical reviewer unless otherwise noted. All results (including tables and figures) presented in the rest of this review were produced by the FDA medical reviewer unless otherwise noted.

### B. Overview of Materials Consulted in Review

Data files were provided by the applicant and accessible from the FDA Electronic Document Room (EDR) under NDA 19766 S_058. The electronic data submissions were dated: 6/18/02, 9/16/02, 9/23/02, 11/22/02, 1/31/03, 2/3/03, 4/10/03, 4/10/03A, and 4/10/03B (see Overall Data Section IV A above). The first datasets received in the 6/18/02 submission by FDA were unacceptable due to the inclusion of extra observations with unacceptable data. Also the original database did not include a dataset for the primary endpoint, total mortality, as well as for several secondary endpoints. Revised datasets were provided and stored in \\CDSESUB1\N19766\S_058\2002-09-23\crt\datasets.

Part of the HPS data was published in two articles in the journal *Lancet* prior to this submission: MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomized placebo-controlled trial Vol. 360, July 6, 2002, 7-22

MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20536 high-risk individuals: a randomized placebo-controlled trial Vol. 360, July 6, 2002, 23-33

### C. Overview of Methods Used to Evaluate Data Quality and Integrity

The entire study was performed in the United Kingdom. There were no domestic sites for DSI to audit.

The revised data provided in the EDR was the database used to produce results presented in Oxford's Lancet publication of HPS (Vol. 360, 2002, pages 7-22). These results did not precisely match the results presented in the study report for the NDA because the database was further updated June 21, 2002, after submission of the NDA. The final labeling was updated to match the published data.

Results computed by the reviewers were checked against revised tables provided by the applicant where possible. Results presented in the labeling were checked and confirmed by the reviewers.

### D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Yes.

### E. Evaluation of Financial Disclosure

The applicant submitted FORM FDA 3454 (3/99): Certification: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS for all clinical investigators involved in the Heart Protection Study from Feb, 1999 to Aug 2001. A total of 201/276= 73% of the clinical investigators were certified as not having entered into any financial arrangements with the applicant, not having proprietary interest in the product or significant equity in the applicant, and not having received any significant payments from the applicant. Out of the remaining 75 investigators, 70 could not be reached because they were no longer at the site and 5 did not return the requested information. With such a large trial including over 20,000 patients from 69 different sites it is unlikely that these investigators could have biased the outcome of this double blind placebo controlled trial. The largest hospital in this trial enrolled 823 pts or 4% of the total patient population. So each investigator saw only a small fraction of the enrolled patients.

## VI. Integrated Review of Efficacy

### A. Brief Statement of Conclusions

- HPS showed that simvastatin 40 mg/day significantly reduced total and CHD mortality, non-fatal MIs, stroke, revascularization procedures and events for two composite endpoints: major coronary events (MCE) comprised of CHD mortality and non-fatal myocardial infarction (NFMI); and major vascular events (MVE) comprised of MCE, stroke and revascularization procedures

- Generally, in pre-specified subgroups, statistically significant treatment effects were observed with relative risk reductions consistent with the effect observed for all patients. Some notable subgroup inconsistencies are summarized below.

  - Statistically significant reductions were seen regardless of prior qualifying disease. Results for diabetics with CHD, a high risk group of about 2,000 patients, consistently showed smaller relative risk reductions and less significant results compared to the diabetics without CHD.

  - The event rates for women were consistently lower than for men and, consequently, risk reductions tended to be less significant.

  - Patients 65 years of age and older showed significant reductions in risk for all endpoints. Patients under 65 years of age failed to show benefit from simvastatin treatment for mortality endpoints (both total and CHD) and stroke where their event rates were low but benefit was observed on all other non-fatal endpoints and on the composite endpoints.

  - Results for subgroups defined by LDL-C level at screening generally showed statistically significant risk reductions due to simvastatin treatment, though the results in patients with LDL-C<100mg/dL tended to show smaller and less significant risk reductions than for patients with LDL-C≥100mg/dL. Patients with low LDL-C and high HDL-C did not show a benefit for the composite endpoint MCE but did show borderline significant results for MVE (p=0.05) primarily due to a risk reduction in stroke. In contrast, patients with low LDL-C and low HDL-C, a similarly sized group (n=1575), had highly significant risk reductions (p<.004) for MCE.

  - About 97% of the patients were Caucasian so no analyses by race could be performed.

**B. Detailed Review of Heart Protection Study**
(conducted July 1994 to November 2001)

**1. Study Design**

The Heart Protection Study (HPS), a placebo-controlled, double blind, parallel study, was conducted at 69 clinics in United Kingdom (UK) by the University of Oxford's Clinical Trial Service Unit with financial support from the UK Medical Research Council, British Heart Foundation, Merck & Co. Inc. and Hoffman and La Roche. HPS is a large trial (about 20,000 patients) of a heterogeneous population of patients at risk for a CHD event within 5 years. A 2x2 factorial design (as shown below) was used to allow for separate assessment of the effects of simvastatin and vitamin as well as assessment of the combinations. The daily dose of simvastatin was 40 mg and the vitamins were Vitamin E 600 mg, Vitamin C 250 mg and beta carotene 20 mg.

| | Active Simvastatin | Placebo Simvastatin |
|---|---|---|
| Active Vitamin | **Sim + Vit** | **Vit** |
| Placebo Vitamin | **Sim** | **Placebo** |

After screening, patients were given placebo for 4 weeks followed by 6 weeks of simvastatin alone treatment. The primary purpose of the run-in was to test compliance (≥90% compliance) and weed-out potential dropouts. Patients satisfying the entry criteria were allocated to one of the four groups using a minimization algorithm. Minimization is a covariate-adaptive method which takes into account the distribution of patients already enrolled and minimizes the imbalance of those characteristics across the treatment groups. In HPS, balance was sought on 10 characteristics measured at screening. (See Appendix 1 for the applicant's description of the minimization procedure used). Hence patients were not randomized to treatment in this trial. The protocol stated that patients would be allocated to treatment using stratified randomization. No amendments were made to the protocol stating that a deterministic allocation procedure would be used instead of the protocol-specified stratified randomization.

Patients were treated and followed for a minimum of five years. Follow-up visits were performed at Months 4, 8 and 12 and then every 6 months. Non-fasting blood samples were taken at each of these visits plus the final follow-up visit and assessed for ALT. About 1,000 random samples of these blood samples were taken once a year to assess the lipid profile. Also ~1,000 diabetics were randomly sampled to assess HbA1c on study.

The timeline for HPS is shown in Table 1. Annual interim analyses were performed but the dates for these were not included in the study report submitted to FDA so they are not included in the table.

Table 1. Timeline for HPS

| | |
|---|---|
| [redacted] | First Patient Entered |
| November 1994 | 4S Study Results Published |
| April 1996 | Protocol amended to include patients over 75 years and men treated for hypertension as a qualifying disease |
| [redacted] | Last Patient Entered |
| Feb 1998 | Protocol amended to allow patients to stay on assigned study medication while taking non-study lipid-lowering drug |
| 1999 | First publication of efficacy and safety results |
| Sept 2000 to March 2001 | LDL-C assessment on all patients still on study |
| September 2001 | DAP completed |
| [redacted] | Last Patient Completed |

2. Efficacy Endpoints

The efficacy endpoints used in this study are outlined below. The primary endpoints were defined in the original protocol (dated August, 1994) while the secondary and tertiary endpoints were first described in the data analysis plan (dated September, 2001). All endpoints were analyzed as time-to-first event.

Primary Endpoints:

For simvastatin comparison:

1. Total mortality
2. CHD mortality
3. Non-CHD mortality

For vitamin supplementation comparison:

1. Major coronary events (MCE, time to first one of the following)
   - Definite or probable nonfatal MI
   - CHD mortality
2. CHD mortality

Secondary Endpoints:

For simvastatin comparison

1. Cause specific non-CHD mortality

- Hemorrhagic stroke
- Other stroke
- Other vascular
- Neoplastic
- Respiratory
- Hepatic
- Renal
- Other medical causes
- Suicide
- Other non-medical causes

2. Stroke
   - Total (fatal and nonfatal)
   - Presumed ischemic strokes (not confirmed to be hemorrhagic)
3. MCE
   - First 2 years
   - 3+ years
4. Major Vascular Events (MVE, time to first one of the following)
   - MCE
   - Total Stroke
   - Coronary or noncoronary vascular procedures

Tertiary endpoints:

1. Revascularization procedures
   - Coronary
   - Peripheral and other non-coronary
2. Hospitalization for angina, respiratory disease and gallbladder disease
3. Peripheral macrovascular complications of diabetes
   - Peripheral revascularization procedures
   - Lower limb amputations
   - Leg ulcers

The data analysis plan stated that the MCE and MVE endpoints would be analyzed by numerous subgroups; these subgroups are listed in Appendix 2.

3. Entry Criteria

Eligibility was assessed in the following order:

1. Potentially eligible patients were identified from hospital or health authority computerized records of discharge diagnoses and from lists for special clinics (e.g. diabetes clinics).
2. The coordinating center office were sent the records and then identified potentially eligible patients based on age (40 to 80 with oversampling of older patients), sex (oversampling of females) and disease history (see below; oversampling of patients without CHD ).

3. General practitioners were asked to confirm their view of each patient's eligibility.
4. Eligible patients were asked to attend a screening visit and were further screened by a clinic nurse.
5. During the screening period, patients could discontinue or could be determined to be ineligible due to blood results (baseline plasma cholesterol<135 mg/dL, ALT>1.5xULN, creatinine>2xULN, CK>3xULN)
6. Based on the full lipid profile at screening, the GP was asked to indicate if, for any reason, they felt that the patient should not continue in the study.
7. At the end of the 2-month run-in period, patients could continue on study if they confirmed their consent to participate, had been compliant with study medication during the 2 month Run-in period (took about 90% or more of medication as ascertained by returned unused medication), did not have a major vascular event, did not report new or significant muscle pain, and there were no other reasons for concern about long-term compliance.
8. If the patient was deemed eligible to continue, the coordinating center office was called and provided a final eligibility check. Relevant details about eligibility were recorded directly onto the coordinating center computer. The computer then assigned the study treatment (i.e. active or placebo simvastatin; active or placebo vitamins) for that patient using a minimization algorithm (described in Appendix 1 of this review).

Entry criteria included the following:

- Aged 40 to 80
- Screening cholesterol>130
- No predominant medical problem such as alcohol/drug abuse, psychiatric disorder, senility, severe physical disability, severe heart failure or disease with life expectancy less than 5 years.
- Patients at high risk for CHD mortality over the next five years based on at least one of the following disease histories:
    - MI (definite or probable)
    - Other CHD included the following:
        - Angina (stable or unstable)
        - Previous PTCA or CABG
    - Non-CHD included the following:
        - TIA
        - Ischaemic stroke
        - Carotid endarterectomy or angioplasty
        - Other arterial bypass surgery
        - Amputation for vascular disease
        - Other evidence of peripheral vascular disease (intermittent claudication)
        - Diabetes
        - Treated hypertension in men 65 or older

The following changes to entry criteria were made in April, 1996:

- Age increased from 75 to 80 (wished to increase % of women and patients with CVD or hypertension)
- Men 65 or older with treated hypertension (MVE rate of 12-13% expected in this group)

MI, stroke or hospitalization for angina could not occur within 6 months of the screening visit.

4. Sample Size and Power

With 20,000 patients, HPS is powered at 98% with alpha at 0.01 to detect a 25% risk reduction in total mortality assuming a placebo death rate of about 14% (which is close to the rate of 14.7% observed). A subgroup of 6,000 to 7,000 patients has sufficient power to show a 25% risk reduction in CHD mortality (35% on MCE) assuming a 9% placebo rate and alpha of 0.01. The power to detect a 25% risk reduction with 3000 patients is 80% assuming alpha of .05 and a 12% placebo rate. This trial was clearly powered to show statistically significant effects in a wide range of subgroups.

5. Patient Disposition

A total of 63,603 patients were screened at 69 centers in the UK (Table 2). About half of the screened patients entered the 10-week run-in period. Of the 32,145 patients treated during run-in, about 1/3 (11,609) did not continue into the double-blind treatment period. Of the run-in dropouts, about 10% dropped at the first run-in visit. Over 40% either were lost to follow-up (did not attend allocation visit) or were disqualified at the allocation visit (primarily due to patient wishes). About 16% were considered non-compliant during the run-in or unable to remain compliant long-term. About 10% were considered ineligible due to a blood test result. There was no evidence of systematic bias in the selection of patients to continue into the treatment period. The patient characteristics of patients dropping out during the run-in period were similar to those continuing to treatment allocation. Dropouts were evenly spread across the centers with no center rejecting a large proportion of patients.

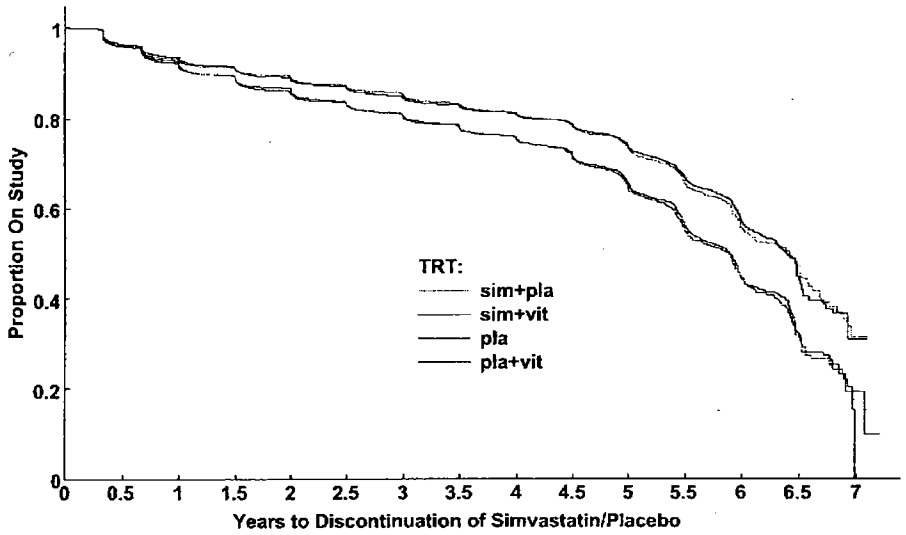
Table 2. HPS Patient Disposition

| | Simvastatin + Placebo | Simvastatin + Vitamin | Placebo | Placebo + Vitamin | Total |
|---|---|---|---|---|---|
| Screened | | | | | 63,603 |
| Entered Run-in | | | | | 32,145 |
| Allocated | 5134 | 5135 | 5133 | 5134 | 20,536 |
| Completed | 3487 (68%) | 3517 (68%) | 3031 (59%) | 2985 (58%) | 12,993 (63%) |

Numbers were extracted from Applicant's Table 5 and Appendix 4.4 of the study report

A total of 20,536 were allocated to the four treatment groups with a total of 10,269 allocated to simvastatin and 10,267 to placebo. A dropout rate of about 41% was seen in the placebo/placebo+vitamin group and about 32% in the simvastatin treated groups. A graph of the time to study discontinuation (Figure 1) shows that placebo or placebo+vitamin treated patients dropped out earlier than the simvastatin treated patients. (Note that the waviness of the curve is due to the fact that patients were usually counted as discontinued at a scheduled visit.)

Figure 1. Proportion of patients on study by time on study for the four treatment groups




In spite of the large dropout rates, endpoint data were available on almost all patients; only 7 patients who left the country were lost-to-follow-up at the end of the study. So at the end of the study, there was near full ascertainment for death and occurrence of cancer; information was also obtained for nonfatal events from available medical records.

The reasons patients who dropped out were similar for the simvastatin groups (simvastatin+placebo and simvastatin+vitamin) and for the placebo groups (placebo+vitamin and placebo) so the data is combined for Table 3 on the following page. The primary reason patients discontinued from the study in both treatment groups was patient request with 22% in the simvastatin group and 26% in the placebo group. In the placebo group, another major reason (13%) for study discontinuation was non-study statin started. Note that four years into the trial the protocol was modified to allow patients to continue on study while taking a non-study statin.

**Table 3. HPS Reasons for discontinuation from double-blind treatment (Applicant's Table 9)**

Table 9

Reason for Discontinuation of Active or Placebo-Simvastatin
(Number and Percentage or Mean ± SD)

| Reason(s) given | Simvastatin Comparison | | | |
|---|---|---|---|---|
| | Active (n=10,269) | | Placebo (n=10,267) | |
| Patient wishes to stop | 2216 | (21.6%) | 2725 | (26.5%) |
| Not willing to attend clinics | 767 | (7.5%) | 838 | (8.2%) |
| Nonstudy statin started[1] | 357 | (3.5%) | 1380 | (13.4%) |
| Other contraindicated drug started | 5 | (0.0%) | 13 | (0.1%) |
| Abnormal liver or muscle enzymes[2] | 55 | (0.5%) | 41 | (0.4%) |
| Both liver & muscle raised | 4 | (0.0%) | 0 | (0.0%) |
| Muscle alone raised | 4 | (0.0%) | 1 | (0.0%) |
| Liver alone raised | 41 | (0.4%) | 32 | (0.3%) |
| Neither liver nor muscle raised | 4 | (0.0%) | 8 | (0.1%) |
| Muscle pain or weakness | 47 | (0.5%) | 50 | (0.5%) |
| Other symptoms | 294 | (2.9%) | 320 | (3.1%) |
| Other reasons | 551 | (5.4%) | 743 | (7.2%) |
| Any of the above[3] | 3265 | (31.8%) | 4253 | (41.4%) |

[1] Protocol modified during study to allow study simvastatin/placebo to be continued with nonstudy statin dose of up to 40 mg daily simvastatin (or approximate equivalent in cholesterol-lowering potential of other statin)
[2] Retrospectively confirmed by raised liver enzymes defined as ALT >1.5 x ULN or GGT >2 x ULN or raised muscle enzymes defined as CK >4 x ULN at one or more of the previous 4 visits or at a non-HPS hospital.
[3] Patient may stop study treatment for more than one reason.
ALT = Alanine aminotransferase; CK = Creatine kinase; GGT = Gamma-glutamyl transferase; HPS = Heart Protection Study; ULN = Upper limit of normal.

6. Baseline Characteristics

Baseline characteristics were measured at the screening visit before the run-in treatment with simvastatin. The allocation of patients to treatment using a minimization procedure provided near perfect balance across the treatment groups (Table 4 on following page, see Appendix 1 for a list of minimization factors). The majority of the patients were Caucasian (97%) and male (75%). About 2/3's of the patients presented with CHD; about 40% of the patients had a prior MI. About 40% of the patients had hypertension and 29% had diabetes.

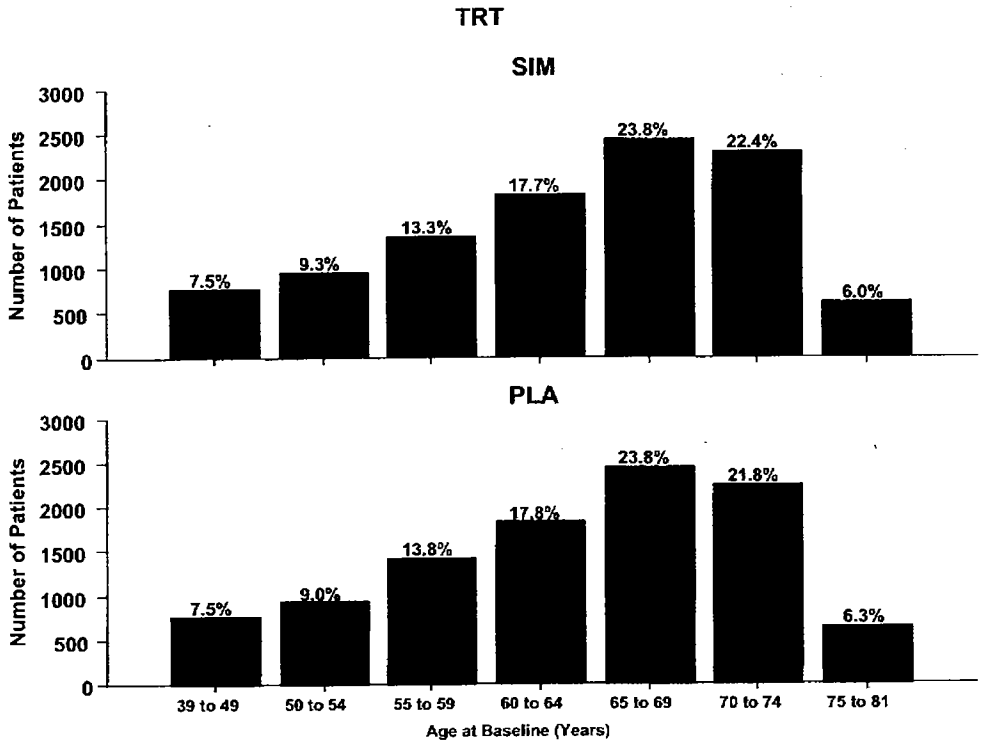
Table 4. HPS Baseline characteristics measured at the initial screening visit

| | Simvastatin (N=10269) | Placebo (N=10267) |
|---|---|---|
| Age (years) | | |
| Mean (SD) | 63.5 (8.4) | 63.5 (8.4) |
| Range | 39-81 | 39-81 |
| ≥65 | 52% | 52% |
| ≥75 | 6% | 6.3% |
| Gender | | |
| Male | 75% | 75% |
| Female | 25% | 25% |
| Race | | |
| Caucasian | 97% | 97% |
| East Indian | 1.6% | 1.6% |
| West Indian | 1% | 1% |
| Other | 0.4% | 0.4% |
| BMI ($kg/m^2$) Mean (SD) | 28 (4) | 28 (4) |
| Smokers | | |
| Never regularly | 25% | 25% |
| Former | 61% | 61% |
| Current | 14% | 14% |
| Prior MI | 41.5% | 41.4% |
| Angina (stable or unstable) | 52% | 53% |
| Previous PTCA | 6.9% | 6.6% |
| Previous CABG | 16% | 15.1% |
| Any CHD | 65% | 65% |
| Diabetes | 29% | 29% |
| Type 1 diabetes | 3% | 3% |
| Type 2 diabetes | 26% | 26% |
| Mean HbA1c for diabetics | 7.1 (2.4) | 7.1 (2.4) |
| Hypertension (treated) | 41% | 41% |
| Cerebrovascular Disease | 16% | 15,.9% |
| Peripheral Vascular Disease | 33% | 32.8% |
| Mean Screening Lipids (SD) mg/dL | | |
| TC | 226 (40) | 226 (39) |
| LDL-C | 131 (32) | 131 (32) |
| HDL-C | 41 (13) | 41 (13) |
| TG (median) | 155 | 155 |
| Apo A1 | 120 (22) | 120 (22) |
| Apo B | 114 (23) | 114 (23) |
| Mean Blood Pressure (SD) | | |
| Diastolic | 81 (12) | 81 (12) |
| Systolic | 144 (24) | 144 (23) |
| Medication Use[1] | | |
| Ace Inhibitors | 19.4% | 19.4% |
| Beta Blockers | 25.9% | 25,5% |
| Calcium Channel Blockers | 31.1% | 31.9% |
| Aspirin | 63.1% | 63.3% |

1 Measured at the allocation visit at the end of the run-in

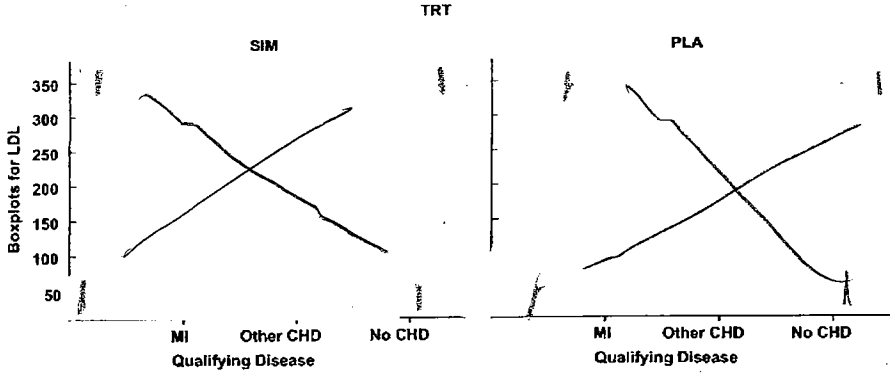
About half of the patients in this trial were over 65 years. Among the patients under 65, about 70% are 55 to 64 and about 30% are 60 to 64 (Figure 2). Near the end of recruitment after increasing the age limit for study entry from 75 to 80; the applicant was able to recruit about 1200 patients over 75.

Figure 2. Baseline age (years) distribution




Lipids measured at screening before the run-in period were well balanced between the treatment groups (Table 4). Boxplots of LDL-C show the wide range of LDL-C values regardless of qualifying disease at entry; 16.7% of the patients had LDL-C values less then 100.

Figure 3. LDL-C (mg/dL) measured at the screening visit, by qualifying disease



7. Statistical Methods for Analysis of Efficacy Endpoints

All analyses were performed on an intent-to-treat (ITT) population. Patients, then, who stopped or switched medications were analyzed as part of their assigned treatment group.

Tests of interaction to determine the contribution of vitamins on the effect of simvastatin were performed by the applicant but not presented in the study report so the FDA reviewer also performed these analyses. Lack of a significant interaction allows for combining of all patients on active simvastatin for comparison to all patients on placebo (placebo/placebo and placebo/vitamins) for the endpoint analyses.

All efficacy endpoints were time-to-event endpoints and were analyzed by the applicant and this reviewer using the log rank test as specified in the protocol. No covariates were included in the analysis model. Given the large size of this trial, it is unlikely that the addition of covariates would increase the power of the statistical test in any measurable amount. Nevertheless this reviewer ran several models using various covariates (particularly those used for minimization). These exploratory analyses showed no impact on results due to the inclusion of covariates in the model.

No adjustment for multiplicity on primary endpoints was planned; all tests were at alpha of .05. The protocol specified adjustment for multiplicity using a 10-fold Bonferroni correction for analyses of 10 causes of death (a secondary endpoint). It is interesting that a stringent adjustment was planned for these outcomes where the primary objective was to show no difference. Needless to say, it was not necessary to make these adjustments. No adjustments were planned for any of the other secondary or tertiary endpoints.

Numerous subgroup analyses were planned (see Appendix 2 for a list) with no adjustments for multiple comparisons. Large subgroups (6,000 or more patients) were expected to show significant treatment effects. Actually with about 3,000 patients there is sufficient power (80%) to detect a risk reduction of 25% for event rates of 12% or greater. This reviewer thinks that significant effects should also be observed in groups of patients not previously recommended for statin therapy (e.g. non-CHD patients with low LDL-C). To test consistency of effect across subgroups, the applicant ran tests for heterogeneity and trend.

Interim analyses on mortality and major morbidity were planned at least annually. A data monitoring committee assessed these results. The protocol stated that "proof beyond reasonable doubt" would be needed to modify the trial in any way. No formal stopping rules were defined in the protocol. The timing of results of the interim analyses were not provided in the study report.

The applicant presented results as summary statistics, number (percent) of cases, observed minus expected patients with events in the active treatment group and its variance, the z statistic for assessing the statistical significance level of the result, along with risk ratios, and 95% CI on the risk ratios were presented for all outcome endpoints.

This reviewer has crafted tables of results that contain some of the information provided by the applicant but in a format consistent with past FDA reviews of large lipid trials. Subgroups were chosen for display based on the relevance to this study and to be consistent with results presented for other reviewed studies. Numerous other subgroups were analyzed by the reviewer to ascertain that results were consistent for protocol-defined subgroups and for all subgroups mentioned in the proposed labeling.

A few terms used in the tables require explanation. Other CHD includes angina (stable or unstable), previous PTCA and previous CABG. No CHD includes hypertension, diabetes, TIA, ischaemic stroke, carotid endarterectomy or angioplasty, other arterial bypass surgery, amputation for vascular disease and other evidence of peripheral vascular disease. With regard to smoking, patients were asked if they "ever smoked cigarettes regularly" so there was no strict category of "never smoked". Hypertension refers to patients who were being treated for diagnosed hypertension.

8. Compliance and Use of Non-study statins

Overall compliance was assessed from compliance to the allocated treatment regimen and from the use of non-study statins.

Compliance to the allocated treatment regimen was measured at each scheduled visit by counting returned medication. Patients taking 80% or more of their medication were considered compliant; most patients taking less than 80%, actually took less than 10% of their allocated medication. The applicant did not compute an overall compliance value for each patient. Instead the average compliance computed at each visit were combined weighting on the standard error to obtain a study average. The study average in the simvastatin group was 82% and in the placebo group, 76%. Compliance tended to decrease over time in both treatment groups.

The use of non-study statins changed during the course of the study primarily due to modifications to the protocol. Under the original protocol, patients were not eligible to enter HPS if they were on lipid lowering medication and were removed from the study if their physician decided that non-study statin medication was warranted (though they continued to be followed). About 4% of simvastatin patients and 13% of placebo patients dropped during the study due to the use of non-study statins. In 1998, 4 years into the study and 1 year after the last patient was recruited, the protocol was modified to allow patients to remain on allocated treatment while taking non-study statins. As for compliance, the applicant computed a study average for non-study statin use; for the simvastatin group the average was 5% and for the placebo group, 17.5%. At the final visit, 11.5% (992/8590) of the remaining simvastatin patients and 35.9% (3010/8378) of the remaining placebo patients were taking non-study statins; simvastatin was the most commonly taken non-study statin.

Using both compliance and non-study statin use, the applicant computed the average use of simvastatin in both groups. The average use in the simvastatin group was 84.9% and in the placebo group, 17.5%. The study report states the following:

> "The average 15.1% of participants allocated simvastatin but not taking it, ... and the average 17.5% of the participants allocated placebo taking non-study statin, combine to a total of 32.6% of participants who effectively did not contribute to the comparison of the allocated treatments." Page 119 of the HPS study report

This statement is not saying 32.6% of the patients are non-compliant since actually 16.3% of the total population were noncompliant as the calculations below show.

15.1% of the simvastatin patients = .151x10,269 = 1,551 patients out of 10,269
17.5% of the placebo patients = .175x10,267 = 1,797 patients out of 10,267

total 1551+1797 / 10269+10267 x100 = **16.3%**

The 1/3 estimate of net noncompliance refers to the proportion that contribute to a null effect. Simple algebra by this reviewer illustrates the assumptions made to compute the effect adjusted for noncompliance.

> Assuming the observed effects are 12% for placebo and 9% for simvastatin, one could find the "true" rates (i.e. the observed rates adjusted for noncompliance) by solving the following algebraic equations for PS ("true" simvastatin rate) and PP ("true" placebo rate):
>
> (0.175) PS + (0.825) PP=0.12
> (0.85) PS + (0.15) PP =0.09
>
> PS=8.3% and PP=12.8% yielding a RRR=35%

Adjusting for noncompliance increases the relative risk reduction (RRR) from 24% to 35%, though , one must assume that the noncompliers exhibit the rate of the treatment group they have not been allocated to. In a time-to-event analysis, this may not be a reasonable assumption since it matters when the noncompliance occurs with respect to the occurrence of an event. Furthermore, noncompliance may be related to outcome. For HPS, this is particularly likely given the publication of 4S and its impact on the use of statins in a secondary prevention population.

Another way to look at the effect on noncompliance might be to look at the applicant's analysis of the event rates by year to see if the risk reductions decreased as overall compliance decreased. However, the applicant's analysis is flawed in that only the first event experienced by a patient is counted in all the analyses. For example, if a patient had an event in Year 2 and another one in Year 4, only the event in Year 2 is included; the analysis of the Year 4 data does not include the

Year 4 event. The elimination of events that occur later from the by-year analyses may bias against picking up later differences. For the MVE endpoint, there were 325 simvastatin MVE events and 548 placebo MVE events not considered in the by-year analyses. Note that for each patient only one event should be counted for each yearly analysis and in the overall analyses of multiple years. To appreciate the risks at each year all the first events for that year should be counted; without doing so, the effect of noncompliance in the later years of the trial cannot be ascertained.

There is not sufficient information to conclude with any confidence that the estimates from the ITT analyses are underestimates of the effects of simvastatin and that lack of compliance had any notable effects on the trial results.

9. Contribution of Vitamins by Tests of Interaction

To determine if the addition of vitamins to simvastatin had an impact on the effect of simvastatin, the interaction of simvastatin and vitamins is assessed; there was sufficient power in HPS to test for an interaction. The results (Table 5) clearly show that vitamins had essentially no effect on the outcomes of total and CHD mortality and on the composite endpoints, MCE and MVE with all p-values greater than .05. Given these results, it is sensible to combine the two active simvastatin groups and the two placebo groups.

Table 5. Results for tests of interaction for four endpoints

| | Simvastatin + Placebo | Simvastatin + Vitamin | Placebo | Placebo + Vitamin | p-value interaction |
|---|---|---|---|---|---|
| Total Mortality | 656/5134 13% | 672/5135 13% | 733/5133 14% | 774/5134 15% | .70 |
| CHD Mortality | 280/5134 5.5% | 307/5135 6% | 350/5133 7% | 357/5134 7% | .51 |
| MCE | 446/5134 9% | 452/5135 9% | 601/5133 12% | 611/5134 12% | .995 |
| MVE | 1019/5134 20% | 1014/5135 20% | 1293/5133 25% | 1292/5134 28% | .857 |

**10.** Efficacy Analyses

**Primary Endpoint: Total Mortality**

Simvastatin significantly reduced the risk of mortality for any reason with a relative risk reduction of 13% (log rank, p=.0003) and a difference in event rates of 1.8% (Table 7 on the following page). Kaplan-Meier survival curves show no difference between the curves during the first 2-3 years of the trial but increasing differences with time (Figure 4).

**Figure 4. Survival Curves for Total Mortality**

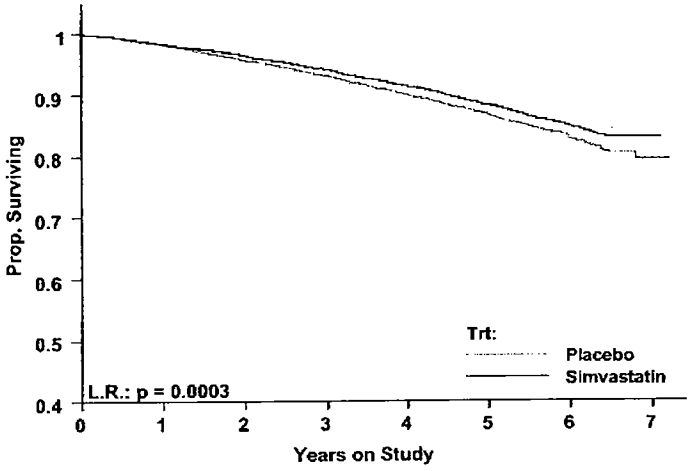



Table 6 shows the causes of death by treatment groups for all patients and then broken down for patients presenting with and without CHD at entry. The primary cause of death in both treatment groups was coronary disease with about half the deaths; the second most prevalent cause of death was cancer with slightly more cases in the simvastatin group, particularly for non-CHD patients.

Table 6. Cause of Death

| | Simvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | All Pts (n=10269) | CHD Pts (n=6694) | Non-CHD Pts (n=3575) | All Pts (n=10267) | CHD Pts (n=6692) | Non-CHD Pts (n=3575) |
| All causes | 1328 (12.9%) | 926 (13.8%) | 402 (11.2%) | 1507 (14.7%) | 1048 (15.7%) | 459 (12.8%) |
| Coronary | 587 (5.7%) | 466 (7.0%) | 121 (3.4%) | 707 (6.9%) | 554 (8.3%) | 153 (4.3%) |
| Other Vas. | 194 (1.9%) | 120 (1.8%) | 74 (2.1%) | 230 (2.2%) | 123 (3.6%) | 107 (3.0%) |
| Cancer | 359 (3.5%) | 210 (3.1%) | 149 (4.2%) | 345 (3.4%) | 241 (3.6%) | 104 (2.9%) |
| Respiratory | 90 (0.9%) | 64 (1.0%) | 26 (0.7%) | 114 (1.1%) | 68 (1.0%) | 46 (1.3%) |
| Other Med. | 82 (0.8%) | 53 (0.8%) | 29 (0.8%) | 90 (0.9%) | 52 (0.8%) | 38 (1.1%) |
| Non-med | 16 (0.2%) | 13 (0.2%) | 3 (0.1%) | 21 (0.2%) | 10 (0.2%) | 11 (0.3%) |

Table 7. Total Mortality results for all patients and by subgroups

| | Simvastatin | Placebo | RR | 95% CI | P-value |
|---|---|---|---|---|---|
| All patients | 1328/10269 (12.9%) | 1507/10267 (14.7%) | 0.87 | 0.81, 0.94 | .0003 |
| Gender | | | | | |
| Male | 1102/7727 (14.3%) | 1245/7727 (16.1%) | 0.88 | 0.81, 0.95 | .001 |
| Female | 226/2542 (8.9%) | 262/2540 (10.3%) | 0.86 | 0.72, 1.02 | .09 |
| Age at Baseline | | | | | |
| <65 | 365/4903 (7.4%) | 418/4936 (8.5%) | 0.87 | 0.76, 1.01 | .06 |
| 65-70 | 361/2447 (14.8%) | 413/2444 (16.9%) | 0.87 | 0.75, 0.997 | .045 |
| 70 to <75 | 461/2304 (20%) | 484/2239 (21.6%) | 0.92 | 0.81, 1.04 | .18 |
| ≥75 | 141/615 (22.9%) | 192/648 (29.6%) | 0.75 | 0.60, 0.93 | .009 |
| By tertiles | | | | | |
| <60 | 167/3082 (5.4%) | 185/3110 (6.0%) | 0.91 | 0.74, 1.12 | .38 |
| 60-68 | 465/3807 (12.2%) | 549/3779 (14.5%) | 0.83 | 0.73, 0.94 | .003 |
| >68 | 696/3380 (20.6%) | 773/3378 (22.9%) | 0.89 | 0.80, 0.98 | .02 |
| Qualifying disease | | | | | |
| Prior MI | 672/4257 (15.8%) | 749/4253 (17.6%) | 0.89 | 0.80, 0.99 | .03 |
| Other CHD | 254/2437 (10.4%) | 299/2439 (12.2%) | 0.84 | 0.71, 0.996 | .045 |
| No CHD | 402/3575 (11.2%) | 459/3575 (12.8%) | 0.87 | 0.76, 0.99 | .04 |
| Smoking | | | | | |
| Never regularly | 236/2594 (9.1%) | 256/2580 (9.9%) | 0.91 | 0.76, 1.09 | .30 |
| Former | 849/6229 (13.6%) | 1004/6220 (16.1%) | 0.84 | 0.76, 0.92 | .0001 |
| Current | 243/1446 (16.8%) | 247/1467 (16.8%) | 1.0 | 0.84, 1.19 | .98 |
| Screening LDL-C mg/dL | | | | | |
| <100 | 223/1720 (13.0%) | 240/1701 (14.1%) | 0.92 | 0.77, 1.1 | .36 |
| 100 to <130 | 449/3536 (12.7%) | 534/3532 (15.1%) | 0.82 | 0.73, 0.93 | .003 |
| ≥130 | 656/5013 (13.1%) | 733/5034 (14.6%) | 0.89 | 0.81, 0.99 | .04 |
| Diabetes | | | | | |
| Yes | 384/2978 (12.9%) | 446/2985 (14.9%) | 0.85 | 0.74, 0.97 | .02 |
| w/CHD | 204/972 (21%) | 225/1009 (22.3%) | 0.92 | 0.76, 1.1 | .40 |
| w/o CHD | 180/2006 (9%) | 221/1976 (11.2%) | 0.79 | 0.65, 0.97 | .02 |
| No | 944/7291 (13.0%) | 1061/7282 (14.6%) | 0.88 | 0.81, 0.96 | .005 |
| w/CHD | 722/5722 (12.6%) | 823/5683 (14.5%) | 0.87 | 0.78, 0.96 | .005 |
| w/o CHD | 222/1569 (14.1%) | 238/1599 (14.9%) | 0.94 | 0.79, 1.13 | .53 |
| Hypertension | | | | | |
| Yes | 582/4211 (13.8%) | 721/4246 (17%) | 0.80 | 0.71, 0.89 | <.0001 |
| No | 746/6058 (12.3%) | 786/6021 (13%) | 0.94 | 0.85, 1.04 | .24 |

In all subgroups, a smaller incidence rate was observed for simvastatin compared to placebo with the exception of current smokers where no difference was observed (Table 7). The wide range of placebo rates from 6.0% for patients under 60 to over 20% for patients over 68 and for diabetics with CHD reflect the heterogeneity of the population. Statistically significant benefits were observed for most groups with some notable exceptions. Patients without treated hypertension (a large group of over 12,000 patients) showed no difference between the treatment groups (p=.24); this is curious given the make up of the population and the size of the subgroup though it is clear that hypertension is a significant risk factor. No significant benefit was observed for patients with a screening LDL-C of less than 100.

Though the subgroup of patients with diabetes and CHD is small (at least for HPS) with about 2,000 patients, the risk is very high in this group and so it is disconcerting to see such a small risk reduction (1.3% in absolute risk and 8% in relative risk reduction).

**Primary Endpoint: CHD Mortality**

In addition to total mortality being named as a primary endpoint, both CHD mortality and non-CHD mortality were named as primary endpoints. Only CHD mortality results are presented in this review. The results for non-CHD mortality showed no significant treatment differences.

A statistically significant difference in CHD mortality was observed with an overall event rate of 5.7% for simvastatin and 6.9% for placebo (relative risk reduction of 18%, p=.0005, Table 8 and Figure 5).

**Figure 5. Survival Curves for the Primary Endpoint CHD Mortality**

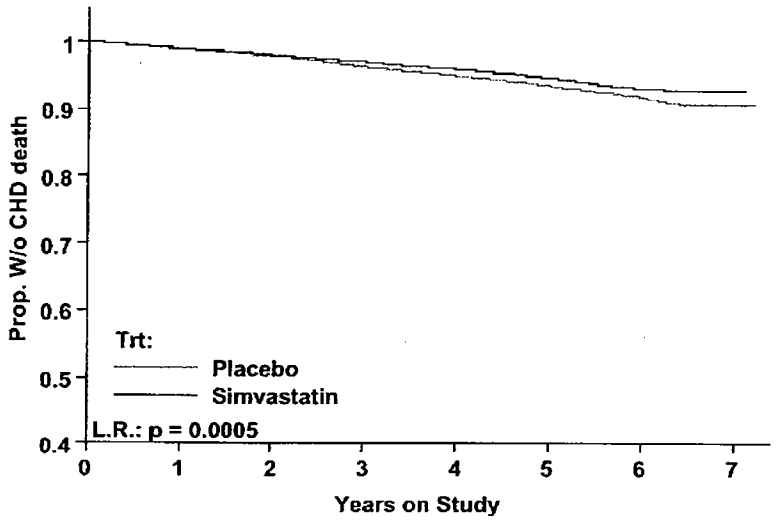


Table 8. CHD Mortality results for all patients and by subgroups

| | Simvastatin | Placebo | RR | 95% CI | P-value |
|---|---|---|---|---|---|
| All patients | 587/10269 (5.7%) | 707/10267 (6.9%) | 0.82 | 0.74, 0.92 | .0005 |
| Gender | | | | | |
| Male | 593/7727 (7.7%) | 506/7727 (6.6%) | 0.85 | 0.75, 0.95 | .006 |
| Female | 81/2542 (3.2%) | 114/2540 (4.5%) | 0.71 | 0.53, 0.94 | .02 |
| Age at Screening | | | | | |
| <65 | 176/4903 (3.6%) | 214/4936 (4.3%) | 0.82 | 0.68, 1.01 | .06 |
| 65-70 | 164/2447 (6.7%) | 198/2444 (8.1%) | 0.82 | 0.67, 1.01 | .06 |
| 70 to <75 | 187/2304 (8.1%) | 215/2239 (9.6%) | 0.84 | 0.69, 1.01 | .08 |
| ≥75 | 60/615 (9.8%) | 80/648 (12.4%) | 0.77 | 0.55, 1.07 | .12 |
| By tertiles | | | | | |
| <60 | 88/3082 (2.9%) | 100/3110 (3.2%) | 0.89 | 0.67, 1.18 | .41 |
| 60-68 | 211/3807 (5.5%) | 269/3779 (7.1%) | 0.77 | 0.64, 0.92 | .004 |
| >68 | 288/3380 (8.5%) | 338/3378 (10%) | 0.84 | 0.72, 0.99 | .03 |
| Qualifying disease | | | | | |
| Prior MI | 361/4257 (8.5%) | 413/4253 (9.7%) | 0.87 | 0.75, 0.99 | .05 |
| Other CHD | 105/2437 (4.3%) | 141/2439 (5.8%) | 0.74 | 0.57, 0.95 | .02 |
| No CHD | 121/3575 (3.4%) | 153/3575 (4.3%) | 0.78 | 0.62, 0.995 | .045 |
| Smoking | | | | | |
| Never regularly | 124/2594 (4.8%) | 137/2580 (5.3%) | 0.89 | 0.70, 1.14 | .37 |
| Former | 379/6229 (6.1%) | 465/6220 (7.5%) | 0.81 | 0.70, 0.92 | .002 |
| Current | 84/1446 (5.8%) | 105/1467 (7.2%) | 0.81 | 0.61, 1.08 | .15 |
| Screening LDL-C mg/dL | | | | | |
| <100 | 97/1720 (5.6%) | 99/1701 (5.8%) | 0.96 | 0.73, 1.3 | .83 |
| 100 to <130 | 182/3536 (5.2%) | 252/3532 (7.1%) | 0.71 | 0.59, 0.86 | .0004 |
| ≥130 | 308/5013 (6.1%) | 356/5034 (7.1%) | 0.86 | 0.74, 1.01 | .06 |
| Diabetes | | | | | |
| Yes | 139/2978 (6.5%) | 239/2985 (8.0%) | 0.80 | 0.66, 0.96 | .02 |
| w/CHD | 119/972 (12.2%) | 145/1009 (14.3%) | 0.84 | 0.66, 1.06 | .14 |
| w/o CHD | 74/2006 (3.7%) | 94/1976 (4.8%) | 0.77 | 0.57, 1.04 | .09 |
| No | 394/7291 (5.4%) | 468/7282 (6.4%) | 0.84 | 0.73, 0.96 | .009 |
| w/CHD | 347/5722 (6.1%) | 409/5683 (7.2%) | 0.84 | 0.73, 0.97 | .02 |
| w/o CHD | 47/1569 (3.0%) | 59/1599 (3.7%) | 0.81 | 0.55, 1.18 | .27 |
| Hypertension | | | | | |
| Yes | 279/4211 (6.6%) | 353/4246 (8.3%) | 0.78 | 0.67, 0.92 | .002 |
| No | 308/6058 (5.1%) | 354/6021 (5.9%) | 0.86 | 0.74, 1.01 | .06 |

Results of subgroup analyses for CHD mortality (Table 8 above) show patterns of response similar to total mortality; all subgroups show a lower CHD death rate for simvastatin than placebo with most showing a highly statistically significant effect ($p<.0001$). No statistically significant treatment effect is seen for patients with LDL-C<100 ($p=.83$) and for patients 60 or younger ($p=.41$). The results for diabetics are barely significant (RRR=20%, $p=.02$) with a larger relative risk reduction observed for non-CHD patients (23%) than CHD patients (16%) though the placebo rate for diabetics with CHD (14.3%) is almost 3 times the rate of the diabetic non-CHD patients (4.8%).

**Secondary Endpoint: Major Coronary Events (MCE)**

The secondary endpoint, major coronary events (MCE), is a composite endpoint of CHD mortality and nonfatal MI (Table 9). Both components contributed to the highly significant relative risk reduction of 27% ($p<.0001$) observed for this endpoint (Figure 6, Tables 9 and 10).

Table 9. Components of MCE (first events only)

| | Simvastatin | Placebo |
|---|---|---|
| Combined | 898/10269 (8.7%) | 1212/10267 (11.8%) |
| CHD Mortality | 541/10269 (5.3%) | 638/10267 (6.2%) |
| Non-fatal MI | 357/10269 (3.5%) | 574/10267 (5.6%) |

An analysis performed by the applicant showed a significant treatment effect after two years of follow-up with an event rate of 4.3% for placebo and 3.4% for simvastatin (Figure 6).

**Figure 6. Survival Curves for MCE**

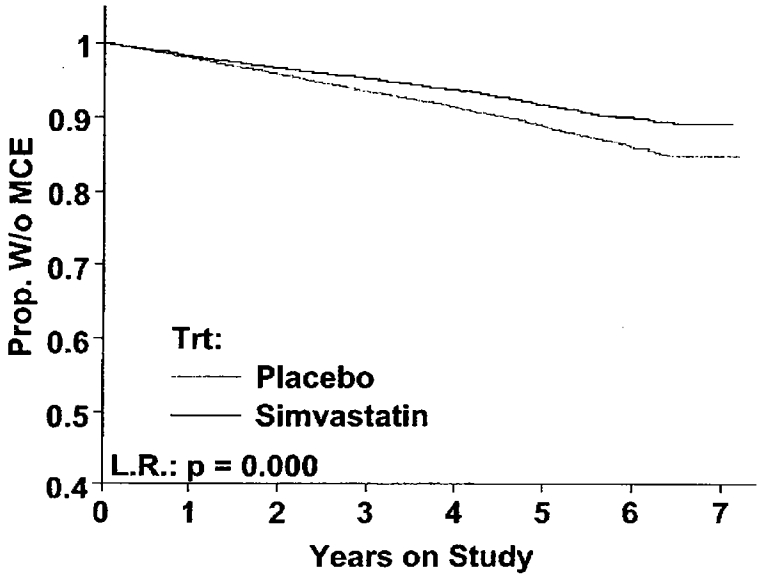


Table 10. MCE results for all patients and by subgroups

| | Simvastatin | Placebo | RR | 95% CI | P-value |
|---|---|---|---|---|---|
| All patients | 898/10269 (8.7%) | 1212/10267 (11.8%) | 0.73 | 0.67, 0.79 | <.0001 |
| Gender | | | | | |
| Male | 767/7727 (9.9%) | 1015/7727 (13.1%) | 0.74 | 0.67, 0.81 | <.0001 |
| Female | 131/2542 (5.2%) | 197/2540 (7.8%) | 0.66 | 0.53, 0.82 | .0002 |
| Age at Baseline | | | | | |
| <65 | 304/4903 (6.2%) | 453/4936 (9.2%) | 0.66 | 0.57, 0.77 | <.0001 |
| 65-70 | 232/2447 (9.5%) | 320/2444 (13.1%) | 0.71 | 0.60, 0.84 | <.0001 |
| 70 to <75 | 280/2304 (12.2%) | 318/2239 (14.2%) | 0.85 | 0.72, 0.997 | .05 |
| ≥75 | 82/615 (13.3%) | 121/648 (18.7%) | 0.68 | 0.51, 0.90 | .006 |
| By tertiles | | | | | |
| <60 | 168/3082 (5.5%) | 245/3110 (7.9%) | 0.68 | 0.56, 0.83 | .0001 |
| 60-68 | 315/3807 (8.3%) | 464/3779 (12.3%) | 0.66 | 0.57, 0.76 | <.0001 |
| >68 | 415/3380 (12.3%) | 503/3378 (14.9%) | 0.81 | 0.71, 0.93 | .002 |
| Qualifying disease | | | | | |
| Prior MI | 539/4257 (12.7%) | 681/4253 (16.0%) | 0.78 | 0.69, 0.87 | <.0001 |
| Other CHD | 178/2437 (7.3%) | 246/2439 (10.1%) | 0.71 | 0.59, 0.86 | .0006 |
| No CHD | 181/3575 (5.1%) | 285/3575 (8.0%) | 0.62 | 0.52, 0.75 | <.0001 |
| Smoking | | | | | |
| Never regularly | 189/2594 (7.3%) | 242/2580 (9.4%) | 0.77 | 0.63, 0.93 | .006 |
| Former | 582/6229 (9.3%) | 763/6220 (12.3%) | 0.75 | 0.67, 0.83 | <.0001 |
| Current | 127/1446 (8.8%) | 207/1467 (14.1%) | 0.61 | 0.49, 0.76 | .006 |
| Screening LDL-C mg/dL | | | | | |
| <100 | 129/1720 (7.5%) | 166/1701 (9.8%) | 0.76 | 0.60, 0.95 | .02 |
| 100 to <130 | 281/3536 (8.0%) | 422/3532 (12.0%) | 0.65 | 0.56, 0.75 | <.0001 |
| ≥130 | 488/5013 (9.7%) | 624/5034 (12.4%) | 0.77 | 0.69, 0.87 | <.0001 |
| Diabetes | | | | | |
| Yes | 279/2978 (9.4%) | 377/2985 (12.6%) | 0.73 | 0.62, 0.85 | <.0001 |
| w/CHD | 169/972 (17.4%) | 212/1009 (21.0%) | 0.81 | 0.66, 0.99 | .04 |
| w/o CHD | 110/2006 (5.5%) | 165/1976 (8.4%) | 0.64 | 0.51, 0.82 | .0003 |
| No | 619/7291 (8.5%) | 835/7282 (11.5%) | 0.73 | 0.66, 0.81 | <.0001 |
| w/CHD | 548/5722 (9.6%) | 715/5683 (12.6%) | 0.75 | 0.67, 0.84 | <.0001 |
| w/o CHD | 71/1569 (4.5%) | 120/1599 (7.5%) | 0.59 | 0.44, 0.79 | .0005 |
| Hypertension | | | | | |
| Yes | 432/4211 (10.3%) | 567/4246 (13.4%) | 0.75 | 0.66, 0.85 | <.0001 |
| No | 466/6058 (7.7%) | 645/6021 (10.7%) | 0.71 | 0.63, 0.80 | <.0001 |

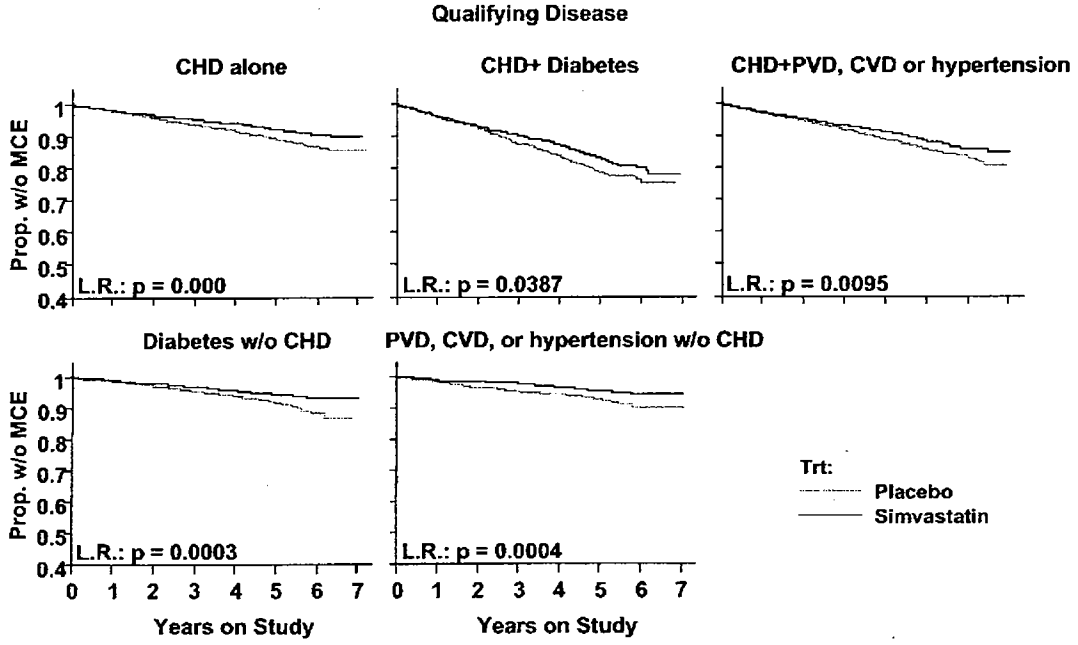
The results of subgroup analyses of MCE ( Table 10) are consistent with the overall relative risk reduction of 27% observed for the general population. Other subgroups that the applicant proposed for analysis were also checked by this reviewer and no notable inconsistencies were found. So when looking at the data by subgroups defined by one factor the results consistently show that simvastatin reduces the risk of CHD death or non-fatal MI across a variety of subgroups. Later in this review there is further discussion of subgroups with regard to LDL-C levels.

Since HPS entered patients based on their qualifying disease and indications are being sought for this heterogeneous group of patients, this reviewer has summarized the MCE results by qualifying disease. Each patient is counted once in this summary, so, for example, a patient with CHD, Diabetes and CVD is counted with the CHD+Diabetes group. Interestingly the strongest effect is seen for the lowest risk group (the patients presenting without CHD but with PVD, CVD and/or hypertension) and the weakest effect for the highest risk group (Diabetes+CHD). Nevertheless, as Figure 7 shows, the treatment effects are significant for each group.

Table 11. MCE by qualifying disease with each patient counted once

| | Simvastatin | Placebo | RR | 95% CI |
|---|---|---|---|---|
| CHD alone | 290/3574 (8.2%) | 415/3623 (11.5%) | 0.70 | 0.60, 0.81 |
| CHD+Diabetes | 169/972 (17.4%) | 212/1009 (21.0%) | 0.81 | 0.66, 0.99 |
| CHD+PVD, CVD and/or hypertension | 258/2175 (11.9%) | 300/2060 (14.6%) | 0.80 | 0.68, 0.95 |
| Diabetes without CHD | 110/2006 (5.5%) | 165/1976 (8.4%) | 0.64 | 0.51, 0.82 |
| PVD, CVD and/or Hypertension w/o CHD | 71/1569 (4.5%) | 120/1599 (7.5%) | 0.59 | 0.44, 0.79 |

**Figure 7. Survival curves for MCE by qualifying disease**

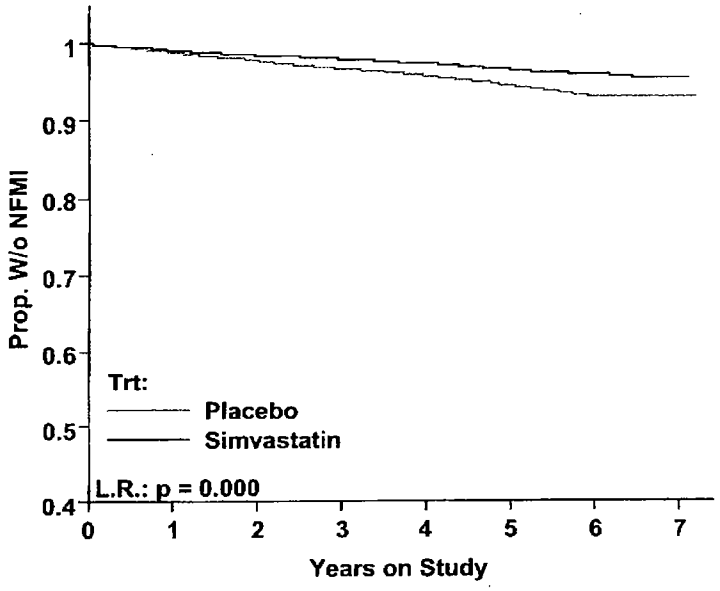


**Secondary Endpoint Non-fatal MI**

Non-fatal MI, was a component of the composite endpoint MCE and contributed almost half the events to MCE. Though not specifically named as a secondary endpoint in the protocol, it is treated here as such because it is an important component of both composite endpoints. According to the study report "the diagnosis of myocardial infarction (MI) required either (1) the presence of 2 or more of: (a) typical ischemic chest pain, pulmonary edema, syncope or shock; (b) development of pathological Q-waves and/or appearance or disappearance of localized ST-elevation followed by T-wave inversion in 2 or more of 12 standard electrocardiograph leads; and (c) increase in concentration of serum enzymes consistent with MI (e.g., CK >2 x upper limit of normal [ULN]); or (2) necropsy findings of MI of an age corresponding to the time of onset of symptoms (silent MIs were not included) " (from Section 5.1 of the NDA study report).

Simvastatin significantly reduced the incidence of non-fatal MI (RRR= 39%, p<.0001, Figure 8 and Table 12).

**Figure 8. Survival Curves for Nonfatal MI**




Sixty-nine placebo patients and 46 simvastatin patients who experienced a non-fatal MI on trial later died of CHD. Patients who entered the trial with a prior MI were at high risk for a second MI (7.4% placebo rate) compared to non-CHD patients (4.1% placebo rate). A highly significant treatment effect was observed for these high risk patients (Table 12, RRR=35%, p<.0001).

Table 12. Nonfatal MI results for all patients and by subgroups

| | Simvastatin | Placebo | RR | 95% CI | P-value |
|---|---|---|---|---|---|
| All patients | 357/10269 (3.5%) | 574/10267 (5.6%) | 0.61 | 0.54, 0.70 | <.0001 |
| Gender | | | | | |
| Male | 298/7727 (3.9%) | 481/7727 (6.2%) | 0.61 | 0.53, 0.70 | <.0001 |
| Female | 59/2542 (2.3%) | 93/2540 (3.7%) | 0.63 | 0.45, 0.87 | .005 |
| Age at Baseline | | | | | |
| <65 | 138/4903 (2.8%) | 262/4936 (5.3%) | 0.52 | 0.42, 0.64 | <.0001 |
| 65-70 | 79/2447 (3.2%) | 140/2444 (5.7%) | 0.55 | 0.42, 0.73 | <.0001 |
| 70 to <75 | 113/2304 (4.9%) | 123/2239 (5.5%) | 0.89 | 0.69, 1.14 | .36 |
| ≥75 | 27/615 (4.4%) | 49/648 (7.6%) | 0.55 | 0.35, 0.89 | .01 |
| By tertiles | | | | | |
| <60 | 84/3082 (2.7%) | 158/3110 (5.1%) | 0.53 | 0.41, 0.69 | <.0001 |
| 60-68 | 118/3807 (3.1%) | 219/3779 (5.8%) | 0.52 | 0.42, 0.65 | <.0001 |
| >68 | 155/3380 (4.6%) | 197/3378 (5.8%) | 0.78 | 0.63, 0.96 | .02 |
| Qualifying disease | | | | | |
| Prior MI | 207/4257 (4.9%) | 315/4253 (7.4%) | 0.65 | 0.54, 0.77 | <.0001 |
| Other CHD | 78/2437 (3.2%) | 114/2439 (4.7%) | 0.67 | 0.51, 0.90 | .007 |
| No CHD | 72/3575 (2.0%) | 145/3575 (4.1%) | 0.49 | 0.37, 0.65 | <.0001 |
| Smoking | | | | | |
| Never regularly | 74/2594 (2.9%) | 116/2580 (4.5%) | 0.63 | 0.47, 0.84 | .002 |
| Former | 231/6229 (3.7%) | 343/6220 (5.5%) | 0.66 | 0.56, 0.78 | <.0001 |
| Current | 52/1446 (3.6%) | 115/1467 (7.8%) | 0.45 | 0.33, 0.63 | <.0001 |
| Screening LDL-C | | | | | |
| mg/dL | 39/1720 (2.3%) | 75/1701 (4.4%) | 0.51 | 0.35, 0.75 | .0006 |
| <100 | 117/3536 (3.3%) | 199/3532 (5.6%) | 0.57 | 0.46, 0.72 | <.0001 |
| 100 to <130 | 201/5013 (4.0%) | 300/5034 (6.0%) | 0.66 | 0.55, 0.79 | <.0001 |
| ≥130 | | | | | |
| Diabetes | | | | | |
| Yes | 105/2978 (3.5%) | 164/2985 (5.5%) | 0.63 | 0.49, 0.80 | .0002 |
| w/CHD | 62/972 (6.4%) | 84/1009 (8.3%) | 0.75 | 0.54, 1.05 | .09 |
| w/o CHD | 43/2006 (2.1%) | 80/1976 (4.1%) | 0.52 | 0.36, 0.75 | .0005 |
| No | 252/7291 (3.5%) | 410/7282 (5.6%) | 0.60 | 0.52, 0.71 | <.0001 |
| w/CHD | 223/5722 (3.9%) | 345/5683 (6.1%) | 0.63 | 0.53, 0.75 | <.0001 |
| w/o CHD | 29/1569 (1.9%) | 65/1599 (4.1%) | 0.45 | 0.29, 0.69 | .0003 |
| Hypertension | | | | | |
| Yes | 184/4211 (4.4%) | 248/4246 (5.8%) | 0.73 | 0.60, 0.89 | .001 |
| No | 173/6058 (2.9%) | 326/6021 (5.4%) | 0.52 | 0.43, 0.63 | <.0001 |

All subgroups showed a significant reduction in non-fatal MI's due to simvastatin treatment, except for diabetics with CHD (a group of 1,981 patients) where the relative risk was 0.75 (95%CI of 0.54 to 1.05, p=.09).

**Secondary Endpoint: MVE**

A second composite endpoint was named in the data analysis plan of major vascular events (MVE). This composite was comprised of the following outcomes: CHD death, non-fatal MI, coronary revascularizations, non-coronary (peripheral) revascularizations, and stroke. The first event experienced by a patient was counted in the analysis of MVE (Table 13). About 60% of the MVE events were coronary events (40% CHD death or nonfatal MI and about 20% coronary revascularization). About 40% of the events were coronary and noncoronary procedures. The addition of procedures and stroke to MCE to create MVE, more than doubled the number of events counted in each treatment group.

Table 13 Components of MVE

| | Simvastatin | Placebo |
|---|---|---|
| Combined | 2033/10269 (19.8%) | 2585/10267 (25.2%) |
| CHD Mortality | 482 | 559 |
| Non-fatal MI | 312 | 503 |
| + Revas | 6 | 11 |
| + Stroke | 4 | 1 |
| Total Stroke | 393 | 505 |
| + Revas | 2 | 8 |
| Cor. Revas. | 425 | 552 |
| Noncor. Revas. | 409 | 446 |

A highly significant treatment effect was seen for MVE with a relative risk reduction of 24% (Figure 9, Table 14 on the following page, p<.0001).

**Figure 9. Survival Curves for MVE**

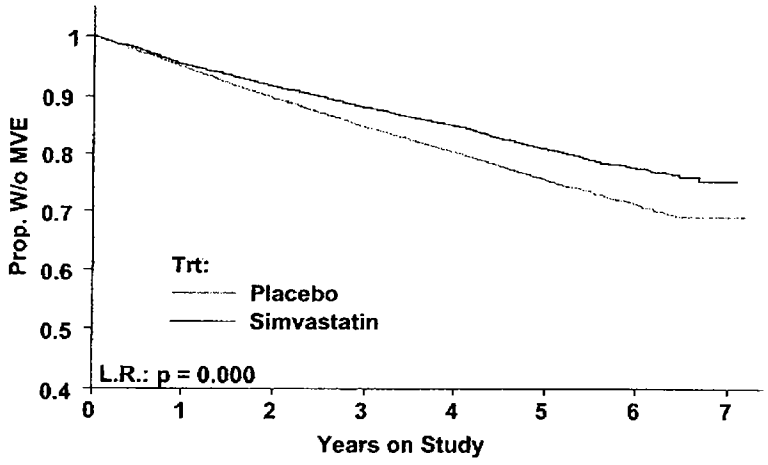


Table 14. MVE results for all patients and by subgroups

| | Simvastatin | Placebo | RR | 95% CI | P-value |
|---|---|---|---|---|---|
| All patients | 2033/10269 (19.8%) | 2585/10267 (25.2%) | 0.76 | 0.72, 0.81 | <.0001 |
| Gender | | | | | |
| Male | 1666/7727 (27.6%) | 1666/7727 (21.5%) | 0.75 | 0.70, 0.80 | <.0001 |
| Female | 367/2542 (14.4%) | 450/2540 (17.7%) | 0.80 | 0.70, 0.92 | .002 |
| Age at Baseline | | | | | |
| <65 | 831/4903 (17.0%) | 1091/4936 (22.1%) | 0.74 | 0.68, 0.82 | <.0001 |
| 65-70 | 512/2447 (20.9%) | 665/2444 (27.2%) | 0.74 | 0.66, 0.83 | <.0001 |
| 70 to <75 | 548/2304 (23.8%) | 620/2239 (27.7%) | 0.84 | 0.74, 0.94 | .002 |
| ≥75 | 142/615 (23.1%) | 209/648 (32.3%) | 0.67 | 0.54, 0.83 | .0002 |
| By tertiles | | | | | |
| <60 | 464/3082 (15.1%) | 629/3110 (20.2%) | 0.73 | 0.64, 0.82 | <.0001 |
| 60-68 | 766/3807 (20.1%) | 980/3779 (25.9%) | 0.75 | 0.68, 0.82 | <.0001 |
| >68 | 803/3380 (23.8%) | 976/3378 (28.9%) | 0.79 | 0.72, 0.87 | <.0001 |
| Qualifying disease | | | | | |
| Prior MI | 999/4257 (23.5%) | 1250/4253 (29.4%) | 0.77 | 0.71, 0.84 | <.0001 |
| Other CHD | 460/2437 (18.9%) | 591/2439 (24.2%) | 0.75 | 0.66, 0.85 | <.0001 |
| No CHD | 574/3575 (16.1%) | 744/3575 (20.8%) | 0.75 | 0.67, 0.84 | <.0001 |
| Smoking | | | | | |
| Never regularly | 406/2594 (15.7%) | 531/2580 (20.6%) | 0.74 | 0.65, 0.84 | <.0001 |
| Former | 1298/6229 (20.8%) | 1638/6220 (26.3%) | 0.76 | 0.71, 0.82 | <.0001 |
| Current | 329/1446 (22.8%) | 416/1467 (28.3%) | 0.79 | 0.68, 0.91 | .001 |
| Screening LDL-C mg/dL | | | | | |
| <100 | 282/1720 (16.4%) | 358/1701 (21.1%) | 0.76 | 0.65, 0.89 | .0006 |
| 100 to <130 | 668/3536 (18.9%) | 871/3532 (24.7%) | 0.74 | 0.67, 0.81 | <.0001 |
| ≥130 | 1083/5013 (21.6%) | 1356/5034 (26.9%) | 0.78 | 0.72, 0.84 | <.0001 |
| Diabetes | | | | | |
| Yes | 601/2978 (20.1%) | 748/2985 (25.1%) | 0.78 | 0.70, 0.87 | <.0001 |
| w/CHD | 325/972 (33.4%) | 381/1009 (37.8%) | 0.86 | 0.74, 0.99 | .04 |
| w/o CHD | 276/2006 (13.8%) | 367/1976 (18.6%) | 0.72 | 0.61, 0.84 | <.0001 |
| No | 1432/7291 (19.6%) | 1837/7282 (25.2%) | 0.75 | 0.70, 0.81 | <.0001 |
| w/CHD | 1134/5722 (19.8%) | 1460/5683 (25.7%) | 0.75 | 0.69, 0.81 | <.0001 |
| w/o CHD | 298/1569 (19.0%) | 377/1599 (23.6%) | 0.79 | 0.67, 0.91 | .002 |
| Hypertension | | | | | |
| Yes | 942/4211 (22.4%) | 1195/4246 (28.1%) | 0.76 | 0.70, 0.83 | <.0001 |
| No | 1091/6058 (18.0%) | 1390/6021 (23.1%) | 0.76 | 0.70, 0.82 | <.0001 |

Each subgroup showed a significant reduction in events for simvastatin compared to placebo with most results highly significant (Table 14, p<.0001). The only group to show borderline results were the diabetics with CHD where a RRR of 14% was observed.

**Secondary Endpoint: Total Stroke**

Total stroke was a composite endpoint of haemorrhagic, ischaemic and subarachnoid haemorrhagic stroke plus strokes of unknown etiology. Table 15 shows that most of the strokes observed in HPS were ischaemic strokes. Treatment with simvastatin leads to a 25% reduction in the risk of total stroke, which is primarily due to a 30% reduction in the risk of ischemic stroke. There is no statistically significant effect on hemorrhagic stroke but clearly the number of events is very small.

**Table 15. Stroke**

| | Simvastatin | Placebo | RR | 95% CI | P-value |
|---|---|---|---|---|---|
| Total Stoke | 444/10269 (4.3%) | 585/10267 (5.7%) | 0.75 | 0.66, 0.85 | <.0001 |
| Haemorrhagic stroke | 39/10269 (0.38%) | 45/10267 (0.44%) | 0.86 | 0.56, 1.32 | 0.49 |
| Ischaemic stroke | 290/10269 (2.8%) | 409/10267 (4.0%) | 0.70 | 0.60, 0.81 | <.0001 |
| Unknown etiology | 143/10269 (1.4%) | 179/10267 (1.7%) | 0.75 | 0.67, 0.85 | <.001 |

**Figure 10. Survival Curves for Total Stroke**

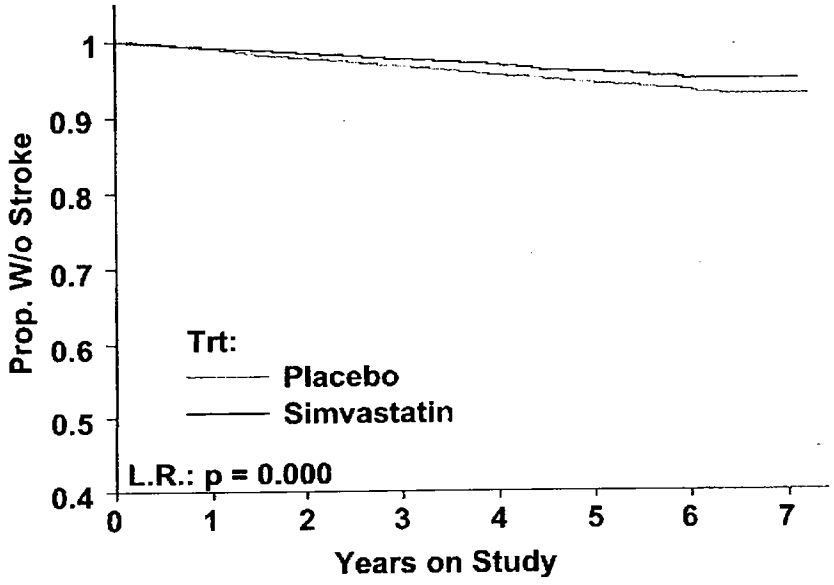


Table 16. Total Stroke results for all patients and by subgroups

| | Simvastatin | Placebo | RR | 95% CI | P-value |
|---|---|---|---|---|---|
| All patients | 444/10269 (4.3%) | 585/10267 (5.7%) | 0.75 | 0.66, 0.85 | <.0001 |
| Gender | | | | | |
| Male | 331/7727 (4.3%) | 453/7727 (5.9%) | 0.72 | 0.62, 0.83 | <.0001 |
| Female | 113/2542 (4.5%) | 132/2540 (5.2%) | 0.85 | 0.66, 1.09 | .19 |
| Age at Baseline | | | | | |
| <65 | 164/4903 (3.3%) | 195/4936 (4.0%) | 0.84 | 0.68, 1.03 | .10 |
| 65-70 | 110/2447 (4.5%) | 154/2444 (6.3%) | 0.70 | 0.55, 0.90 | .004 |
| 70 to <75 | 140/2304 (6.1%) | 167/2239 (7.5%) | 0.80 | 0.64, 1.0 | .054 |
| ≥75 | 30/615 (4.9%) | 69/648 (10.7%) | 0.44 | 0.28, 0.67 | .0001 |
| By tertiles | | | | | |
| <60 | 80/3082 (2.6%) | 101/3110 (3.3%) | 0.80 | 0.60, 1.07 | .13 |
| 60-68 | 172/3807 (4.5%) | 209/3779 (5.5%) | 0.81 | 0.66, 0.98 | .03 |
| >68 | 192/3380 (5.7%) | 275/3378 (8.1%) | 0.68 | 0.57, 0.82 | <.0001 |
| Qualifying disease | | | | | |
| Prior MI | 166/4257 (3.9%) | 221/4253 (5.2%) | 0.74 | 0.61, 0.91 | .003 |
| Other CHD | 99/2437 (4.1%) | 126/2439 (5.2%) | 0.78 | 0.60, 1.01 | .06 |
| No CHD | 179/3575 (5.0%) | 238/3575 (6.7%) | 0.74 | 0.61, 0.90 | .002 |
| Smoking | | | | | |
| Never regularly | 98/2594 (3.8%) | 140/2580 (5.4%) | 0.69 | 0.53, 0.89 | .004 |
| Former | 262/6229 (4.2%) | 345/6220 (5.6%) | 0.75 | 0.64, 0.88 | .0003 |
| Current | 84/1446 (5.8%) | 100/1467 (6.8%) | 0.85 | 0.64, 1.13 | .27 |
| Screening LDL-C | | | | | |
| mg/dL | 69/1720 (4.0%) | 92/1701 (5.4%) | 0.74 | 0.54, 1.01 | .054 |
| <100 | 152/3536 (4.3%) | 211/3532 (6.0%) | 0.70 | 0.57, 0.87 | .001 |
| 100 to <130 | 223/5013 (4.5%) | 282/5034 (5.6%) | 0.79 | 0.66, 0.94 | .007 |
| ≥130 | | | | | |
| Diabetes | | | | | |
| Yes | 149/2978 (5.0%) | 193/2985 (6.5%) | 0.76 | 0.61, 0.94 | .01 |
| w/CHD | 68/972 (7.0%) | 80/1009 (7.9%) | 0.86 | 0.62, 1.19 | .04 |
| w/o CHD | 81/2006 (4.0%) | 113/1976 (5.7%) | 0.69 | 0.52, 0.92 | .01 |
| No | 295/7291 (4.1%) | 392/7282 (5.4%) | 0.74 | 0.64, 0.86 | .0001 |
| w/CHD | 197/5722 (3.4%) | 267/5683 (4.7%) | 0.73 | 0.61, 0.87 | .0006 |
| w/o CHD | 98/1569 (6.3%) | 125/1599 (7.8%) | 0.79 | 0.61, 1.03 | .08 |
| Hypertension | | | | | |
| Yes | 223/4211 (5.3%) | 274/4246 (6.5%) | 0.80 | 0.67, 0.96 | .02 |
| No | 221/6058 (3.7%) | 311/6021 (5.2%) | 0.70 | 0.59, 0.83 | <.0001 |

The simvastatin effect on the event rate for stroke is quite variable across the subgroups with relative risk reductions ranging from a high of 56% in elderly patients (10.7% placebo rate) down to 14% in diabetics with CHD (7.9% placebo rate).

**Tertiary Endpoint: All Revascularization Procedures**

All revascularization procedures included coronary and noncoronary revascularizations. Coronary revascularization included PTCA and CABG. Noncoronary revascularization included carotid and other arterial procedures as well as amputations. Simvastatin significantly reduced both coronary and noncoronary revascularizations with the strongest effect seen for coronary procedures (Table 17). A highly significant relative risk reduction of 24% was seen for all procedures (Table 17 and Figure 11).

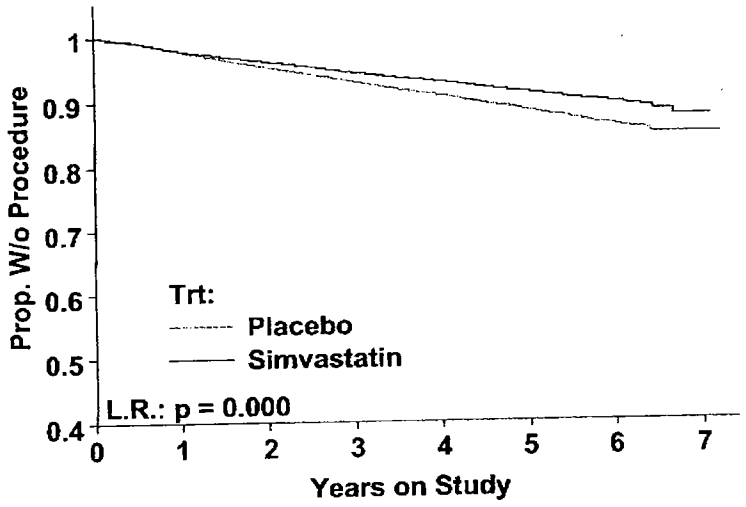
**Table 17. Procedures**

| | Simvastatin N=10269 | Placebo N=10267 | RR | 95% CI | P-value |
|---|---|---|---|---|---|
| All Procedures[1] | 939 (9.1%) | 1205 (11.7%) | 0.76 | 0.70, 0.83 | <.0001 |
| Coronary procedures[1] | 513 (5%) | 725 (7.1%) | 0.69 | 0.62, 0.78 | <.0001 |
| CABG[2] | 322 | 453 | | | |
| PTCA[2] | 210 | 308 | | | |
| Noncoronary procedures[1] | 450 (4.4%) | 532 (5.2%) | 0.84 | 0.74, 0.95 | .005 |

1-First events only 2-All events

For coronary procedures, it is clear from Table 17 that both CABG and PTCA contribute to the treatment effect. For noncoronary procedures, most of the procedures were classified as other arterial procedures.

**Figure 11. Survival Curves for All Revascularization Procedures**



The results for total procedures varies across the subgroups though most subgroups showed significant relative risk reductions (Table 18). Nonsignificant results are seen for women (who have the lowest placebo rate), patients over 75, diabetics with CHD (who have the highest placebo rate) and current smokers.

Table 18. All revascularization procedures results for all patients and by subgroups

| | Simvastatin | Placebo | RR | 95% CI | P-value |
|---|---|---|---|---|---|
| All patients | 939/10269 (9.1%) | 1205/10267 (11.7%) | 0.76 | 0.70, 0.83 | <.0001 |
| Gender | | | | | |
| Male | 782/7727 (10.1%) | 1029/7727 (13.3%) | 0.74 | 0.68, 0.81 | <.0001 |
| Female | 157/2542 (6.2%) | 176/2540 (6.9%) | 0.88 | 0.71, 1.1 | .26 |
| Age at Baseline | | | | | |
| <65 | 473/4903 (9.7%) | 621/4936 (12.6%) | 0.75 | 0.67, 0.85 | <.0001 |
| 65-70 | 230/2447 (9.4%) | 310/2444 (12.7%) | 0.73 | 0.61, 0.86 | .0002 |
| 70 to <75 | 196/2304 (8.5%) | 220/2239 (9.8%) | 0.85 | 0.70, 1.03 | .09 |
| ≥75 | 40/615 (6.5%) | 54/648 (8.3%) | 0.75 | 0.50, 1.13 | .17 |
| By tertiles | | | | | |
| <60 | 277/3082 (9.0%) | 379/3110 (12.1%) | 0.73 | 0.642, 0.85 | <.0001 |
| 60-68 | 376/3807 (9.9%) | 482/3779 (12.8%) | 0.76 | 0.66, 0.87 | <.0001 |
| >68 | 286/3380 (8.5%) | 344/3378 (10.2%) | 0.81 | 0.69, 0.95 | .009 |
| Qualifying disease | | | | | |
| Prior MI | 422/4257 (9.9%) | 561/4253 (13.1%) | 0.74 | 0.65, 0.83 | <.0001 |
| Other CHD | 245/2437 (10.1%) | 307/2439 (12.6%) | 0.78 | 0.66, 0.92 | .004 |
| No CHD | 272/3575 (7.6%) | 337/3575 (9.4%) | 0.79 | 0.68, 0.93 | .005 |
| Smoking | | | | | |
| Never regularly | 161/2594 (6.2%) | 223/2580 (8.6%) | 0.70 | 0.58, 0.86 | .0007 |
| Former | 611/6229 (9.8%) | 795/6220 (12.8%) | 0.75 | 0.67, 0.83 | <.0001 |
| Current | 167/1446 (11.6%) | 187/1467 (12.8%) | 0.90 | 0.73, 1.11 | .32 |
| Screening LDL-C | | | | | |
| mg/dL | 118/1720 (6.9%) | 149/1701 (8.8%) | 0.78 | 0.61, 0.99 | .04 |
| <100 | 305/3536 (8.6%) | 385/3532 (10.9%) | 0.77 | 0.66, 0.90 | .0007 |
| 100 to <130 | 516/5013 (10.3%) | 671/5034 (13.3%) | 0.76 | 0.67, 0.85 | <.0001 |
| ≥130 | | | | | |
| Diabetes | | | | | |
| Yes | 260/2978 (8.7%) | 309/2985 (10.4%) | 0.83 | 0.70, 0.97 | .02 |
| w/CHD | 142/972 (14.6%) | 161/1009 (16.0%) | 0.90 | 0.71, 1.12 | .34 |
| w/o CHD | 118/2006 (5.9%) | 148/1976 (7.5%) | 0.77 | 0.61, 0.98 | .03 |
| No | 679/7291 (9.3%) | 896/7282 (12.3%) | 0.74 | | |
| w/CHD | 525/5722 (9.2%) | 707/5683 (12.4%) | 0.72 | 0.67, 0.82 | <.0001 |
| w/o CHD | 154/1569 (9.8%) | 189/1599 (11.8%) | 0.82 | 0.64, 0.81 | <.0001 |
| | | | | 0.66, 1.01 | .06 |
| Hypertension | | | | | |
| Yes | 402/4211 (9.6%) | 555/4246 (13.1%) | 0.71 | 0.62, 0.80 | <.0001 |
| No | 537/6058 (8.9%) | 650/6021 (10.8%) | 0.81 | 0.73, 0.91 | .0004 |

**Tertiary Endpoint: Hospitalizations (time to first hospitalization)**

As tertiary endpoints, the applicant planned to record time to hospitalization for angina, respiratory disease and gallbladder disease. Only hospitalization for respiratory disease and gallbladder disease. Significant RRR of 17% was seen for all patients; similar reductions are seen for subgroups. Analyses performed by the applicant on angina scores showed no treatment difference.

Table 19. Hospitalizations for angina for all patients and by subgroups

| | Simvastatin | Placebo | RR | 95% CI | P-value |
|---|---|---|---|---|---|
| All patients | 1030/10269 (10.0%) | 1224/10267 (11.9%) | 0.83 | 0.76, 0.90 | <.0001 |
| Gender | | | | | <.0001 |
| Male | 777/7727 (10.1%) | 937/7727 (12.1%) | 0.81 | 0.74, 0.90 | .11 |
| Female | 253/2542 (10%) | 287/2540 (11.3%) | 0.87 | 0.74, 1.03 | |
| Age at Baseline | | | | | |
| <65 | 464/4903 (9.5%) | 575/4936 (11.7%) | 0.80 | 0.71, 0.90 | .0003 |
| 65-70 | 252/2447 (10.3%) | 294/2444 (12.0%) | 0.84 | 0.71, 0.997 | .046 |
| 70 to <75 | 238/2304 (10.3%) | 267/2239 (11.9%) | 0.85 | 0.71, 1.01 | .07 |
| ≥75 | 76/615 (12.4%) | 88/648 (13.6%) | 0.89 | 0.65, 1.21 | .45 |
| By tertiles | | | | | |
| <60 | 293/3082 (9.5%) | 345/3110 (11.1%) | 0.85 | 0.73, 0.99 | .04 |
| 60-68 | 369/3807 (9.7%) | 456/3779 (12.1%) | 0.78 | 0.68, 0.90 | .0005 |
| >68 | 368/3380 (10.9%) | 423/3378 (12.5%) | 0.86 | 0.74, 0.98 | .03 |
| Qualifying disease | | | | | |
| Prior MI | 608/4257 (14.3%) | 738/4253 (17.4%) | 0.80 | 0.72, 0.90 | <.0001 |
| Other CHD | 327/2437 (13.4%) | 353/2439 (14.5%) | 0.92 | 0.79, 1.07 | .25 |
| No CHD | 95/3575 (2.7%) | 133/3575 (3.7%) | 0.71 | 0.54, 0.92 | .009 |
| Smoking | | | | | |
| Never regularly | 223/2594 (8.6%) | 279/2580 (10.8%) | 0.78 | 0.66, 0.93 | .007 |
| Former | 661/6229 (10.6%) | 762/6220 (12.3%) | 0.85 | 0.77, 0.94 | .002 |
| Current | 146/1446 (10.1%) | 183/1467 (12.5%) | 0.80 | 0.64, 0.99 | .04 |
| Screening LDL-C mg/dL | | | | | |
| <100 | 140/1720 (8.1%) | 153/1701 (9.0%) | 0.90 | 0.72, 1.13 | .38 |
| 100 to <130 | 351/3536 (9.9%) | 400/3532 (11.3%) | 0.86 | 0.75, 0.99 | .04 |
| ≥130 | 539/5013 (10.8%) | 671/5034 (13.3%) | 0.79 | 0.71, 0.89 | <.0001 |
| Diabetes | | | | | |
| Yes | 188/2978 (6.3%) | 259/2985 (8.7%) | 0.71 | 0.59, 0.86 | .0003 |
| w/CHD | 140/972 (14.4%) | 188/1009 (18.6%) | 0.74 | 0.60, 0.92 | .007 |
| w/o CHD | 48/2006 (2.4%) | 71/1976 (3.6%) | 0.66 | 0.46, 0.95 | .02 |
| No | 842/7291 (11.6%) | 965/7282 (13.3%) | 0.86 | 0.78, 0.94 | .001 |
| w/CHD | 795/5722 (13.9%) | 903/5683 (15.9%) | 0.86 | 0.78, 0.95 | .002 |
| w/o CHD | 47/1569 (3.0%) | 62/1599 (3.9%) | 0.77 | 0.53, 1.12 | .17 |
| Hypertension | | | | | |
| Yes | 470/4211 (11.2%) | 542/4246 (12.8%) | 0.85 | 0.75, 0.97 | .01 |
| No | 560/6058 (9.2%) | 682/6021 (11.3%) | 0.81 | 0.72, 0.90 | .0002 |

**Tertiary Endpoint: Peripheral macrovascular complications of diabetes**

Peripheral macrovascular complications in diabetics was comprised of peripheral revascularizations (surgery and angioplasty), lower limb amputations and leg ulcers with the most observed events for peripheral revascularization (Table 20). Note that peripheral revascularizations were analyzed as a component of MVE and as a component of total procedures; a highly significant effect was seen on MVE for diabetics while borderline effects were seen for total procedures for diabetics (p=.02).

Table 20. Components of peripheral macrovascular complications

| Type of complication | Simvastatin (n=2978) | Placebo (n=2985) |
|---|---|---|
| Peripheral revascularization | 81 (2.7%) | 109 (3.7%) |
| Lower limb amputation | 41 (1.4%) | 48 (1.6%) |
| Leg ulcer | 34 (1.1%) | 37 (1.2%) |

The overall results in Table 21 show borderline results with a RRR=21% and p=.03. With a sample size of nearly 6,000 patients, these results are not strong. The 95% CI indicates that a relative risk close to one (0.98) are consistent with this data. The results in subgroups are variable which is not surprising given the number of events and the sample sizes across the subgroups. Subgroups with placebo rates greater than 7% show significant or borderline significant effects.

Table 21. Peripheral macrovascular complications of diabetes results for all diabetics and by subgroups of diabetics

| | Simvastatin | Placebo | RR | 95% CI | P-value |
|---|---|---|---|---|---|
| All diabetic patients | 156/2978 (5.2%) | 194/2985 (6.5%) | 0.79 | 0.64, 0.98 | .03 |
| Gender | | | | | |
| Male | 120/2064 (5.8%) | 150/2083 (7.2%) | 0.79 | 0.62, 1.01 | .059 |
| Female | 36/914 (3.9%) | 44/902 (4.9%) | 0.79 | 0.51, 1.22 | .29 |
| Age at Baseline | | | | | |
| <65 | 81/1675 (4.8%) | 98/1696 (5.8%) | 0.82 | 0.61, 1.10 | .19 |
| ≥65 | 75/1303 (5.8%) | 96/1289 (7.5%) | 0.76 | 0.56, 1.02 | .07 |
| Qualifying disease | | | | | |
| Prior MI | 25/560 (4.5%) | 41/565 (7.3%) | 0.60 | 0.36, 0.98 | .04 |
| Other CHD | 31/412 (7.5%) | 29/444 (6.5%) | 1.15 | 0.69, 1.91 | .58 |
| No CHD | 100/2006 (5%) | 124/1976 (6.3%) | 0.78 | 0.60, 1.02 | .07 |
| Screening LDL-C mg/dL | | | | | |
| <100 | 30/676 (4.4%) | 30/669 (4.5%) | 0.98 | 0.59, 1.63 | .94 |
| ≥100 | 126/2302 (5.5%) | 164/2316 (7.1%) | 0.76 | 0.60, 0.95 | .02 |
| Hypertension | | | | | |
| Yes | 54/1196 (4.5%) | 92/1202 (7.7%) | 0.57 | 0.41, 0.80 | .001 |
| No | 102/1782 (5.7%) | 102/1783 (5.7%) | 0.99 | 0.76, 1.31 | .96 |

11. Overall discussion of subgroups

An interesting aspect of the subgroups in HPS is that generally subgroups have a balance in characteristics similar to the overall population although the rates of events can vary considerably. For example, of patients with LDL-C less than 100 and HDL-C>42, 60% had

CHD, similarly patients with LDL-C>130 and HDL-C<35, 65% had CHD at entry. Another example: of patients who never smoked regularly, 62% had a history of CHD while of current smokers, 57% had CHD. So the differences in risk rates can most likely be ascribed to the defining characteristic of the subgroup and generally not to imbalances in other measured characteristics.

HPS was designed specifically to look at subgroups: the trial was overpowered and so there is sufficient power in large subgroups (>3,000) to show a significant effect. There was oversampling at screening in groups often not well-represented (e.g. women, the elderly) and

Table 22. Placebo rates and relative risk reductions[1] by subgroups for five endpoints

| | Total Mortality | | CHD Mortality | | MCE | | MVE | | Stroke | |
|---|---|---|---|---|---|---|---|---|---|---|
| | PLA % | RRR % | PLA % | RRR % | PLA % | RRR % | PLA % | RRR % | PLA % | RRR % |
| Gender | | | | | | | | | | |
| Male | 16.1 | 12 | 6.6 | 15 | 13.1 | 26 | 21.5 | 25 | 5.9 | 28 |
| Female | 10.3 | *14* | 4.5 | [redacted] | 7.8 | 34 | 17.7 | 20 | 5.2 | *15* |
| Age at Baseline By tertiles | | | | | | | | | | |
| <60 | 6.0 | *9* | 3.2 | *11* | 7.9 | 32 | 20.2 | 27 | 3.3 | *20* |
| 60-68 | 14.5 | 17 | 7.1 | 23 | 12.3 | 34 | 25.9 | 25 | 5.5 | [redacted] |
| >68 | 22.9 | [redacted] | 10 | [redacted] | 14.9 | 19 | 28.9 | 21 | 8.1 | 32 |
| Qual. disease | | | | | | | | | | |
| Prior MI | 17.6 | [redacted] | 9.7 | [redacted] | 16 | 22 | 29.4 | 23 | 5.2 | 26 |
| Other CHD | 12.2 | [redacted] | 5.8 | [redacted] | 10.1 | 29 | 24.2 | 25 | 5.2 | *22* |
| No CHD | 12.8 | [redacted] | 4.3 | [redacted] | 8 | 38 | 20.8 | 25 | 6.7 | 26 |
| Smoking | | | | | | | | | | |
| Never reg. | 9.9 | *9* | 5.3 | *11* | 9.4 | 23 | 20.6 | 26 | 5.4 | 31 |
| Former | 16.1 | 16 | 7.5 | 19 | 12.3 | 25 | 26.3 | 24 | 5.6 | 25 |
| Current* | 16.8 | *0* | 7.2 | *19* | 14.1 | 39 | 28.3 | 21 | 6.8 | *15* |
| Screening LDL-C | | | | | | | | | | |
| <100 | 14.1 | *8* | 5.8 | *4* | 9.8 | [redacted] | 21.1 | 24 | 5.4 | [redacted] |
| 100 to <130 | 15.1 | 18 | 7.1 | 29 | 12 | 35 | 24.7 | 26 | 6 | 30 |
| ≥130 | 14.6 | [redacted] | 7.1 | *14* | 12.4 | 33 | 26.9 | 22 | 5.6 | 21 |
| Diabetes | | | | | | | | | | |
| Yes | 14.9 | [redacted] | 8 | [redacted] | 12.6 | 27 | 25.1 | 22 | 6.5 | 24 |
| w/CHD* | 22.3 | *8* | 14.3 | *16* | 21 | [redacted] | 37.8 | [redacted] | 7.9 | [redacted] |
| w/o CHD | 11.2 | [redacted] | 4.8 | *23* | 8.4 | 36 | 18.6 | 28 | 5.7 | 31 |
| No | 14.6 | 12 | 6.4 | 16 | 11.5 | 27 | 25.2 | 25 | 5.4 | 26 |
| w/CHD | 14.5 | 13 | 7.2 | [redacted] | 12.6 | 25 | 25.7 | 25 | 4.7 | 27 |
| w/o CHD | 14.9 | *6* | 3.7 | *19* | 7.5 | 41 | 23.6 | 21 | 7.8 | *21* |
| Hypertension | | | | | | | | | | |
| Yes | 17 | 20 | 8.3 | 22 | 13.4 | 25 | 28.1 | 24 | 6.5 | [redacted] |
| No | 13 | *6* | 5.9 | *14* | 10.7 | 29 | 23.1 | 24 | 5.2 | 30 |

[1] Bolded, italicized and yellow RRR were not significant p>.05, bolded and blue RRR were borderline significant [redacted]. * Sample size<3,000

The results for the subgroups represented in the tables of the review are summarized in Table 22 above. The colors highlight those groups where the results were less robust; clearly most groups

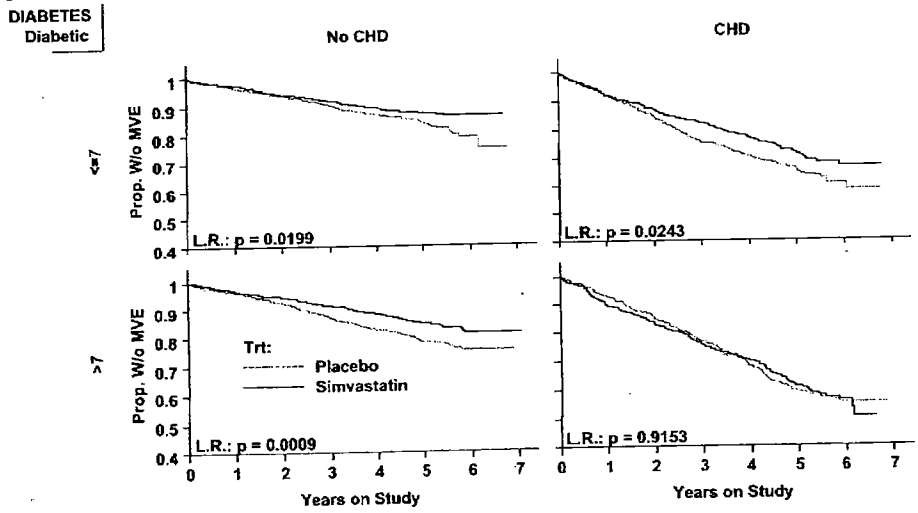
show highly significant effects across the endpoints. The weakest results are seen for patients with LDL-C<100 (discussed in the next section) and diabetics with CHD. Results for diabetes with CHD, a high risk group of about 2,000 patients, consistently showed small relative risk reductions (Table 22) and non-significant results (p>0.09 for mortality endpoints and NFMI) or borderline significant results (p=0.04 for MCE, MVE and stroke) in contrast to the diabetic subgroup without CHD where statistically significant results were seen for all endpoints with relative risk reductions about double the reductions seen for the diabetics with CHD.

In addition to analyzing data for the subgroups represented in the tables, this reviewer looked at all the other subgroups prespecified in the protocol (see Appendix 2). In most subgroups the results are consistent with the overall results.

The applicant made arguments against subgrouping on more than one factor indicating that the event rates would generally be too small to be able to detect an important treatment effect. Nevertheless, this reviewer thought it was important to look at subgroups by more than one factor to either demonstrate the robustness of the results (e.g. consistent effects for diabetics regardless of HbA1c at screening) or to examine subgroups that would be of interest to a practicing physician (e.g. overweight diabetics). In general, the results from these additional analyses show a consistency of effect across a variety of subgroups. The results for a few analyses follow.

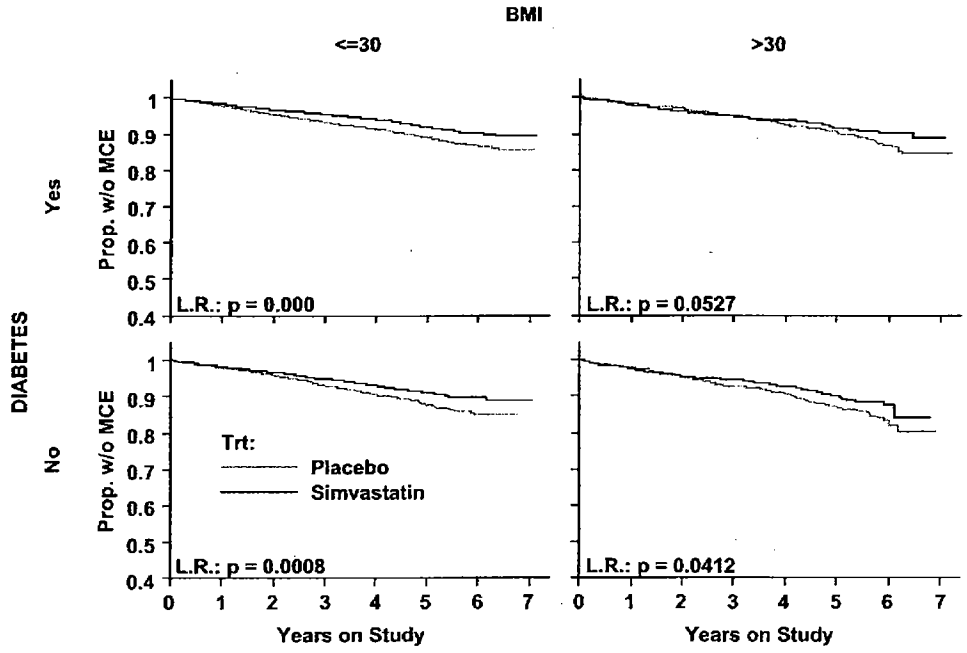
Figure 12 below illustrates that diabetics with CHD and HbA1c greater than 7 at screening have a very high event rate but show no significant treatment effect. Though this subgroup is very small (~800 patients), the results are consistent with other results for diabetics with CHD (i.e. high placebo rates and small RRR).

Figure 12 Kaplan-Meier curves for MVE for diabetics by CHD and HbA1c at screening.



Overweight diabetics are known to be at high risk for coronary events. Though the highest placebo rates are seen for the heaviest patients, the benefits did not differ (Figure 13).

Figure 13 Kaplan-Meier curves for MCE for diabetics by BMI at screening.

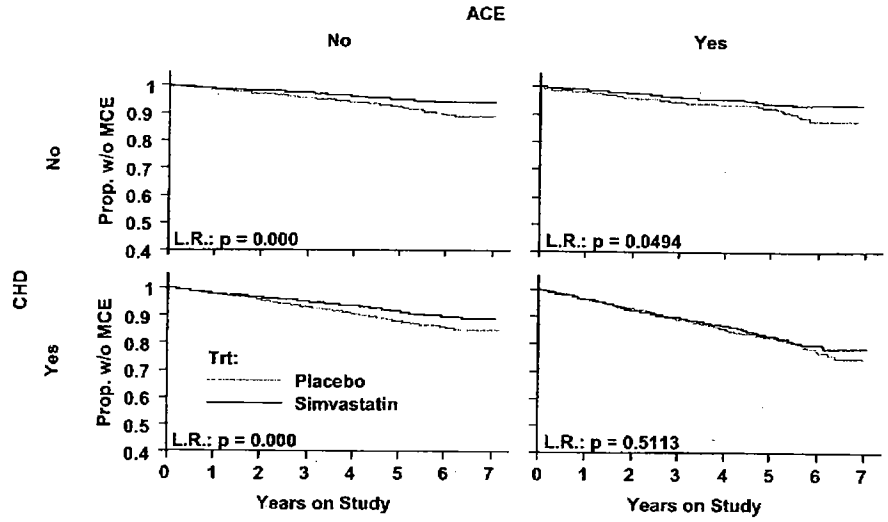



The applicant's test for heterogeneity showed a difference in treatment effect between users of ACE inhibitors and non-users with a larger more significant effect seen for non-users. This reviewer looked at these results by CHD/nonCHD for MCE and found that patients with CHD and taking ACE inhibitors (about 2600 patients) showed essentially no treatment effect (Table 23 and Figure 14 on the following page).

Table 23. MCE results by CHD and ACE inhibitor use

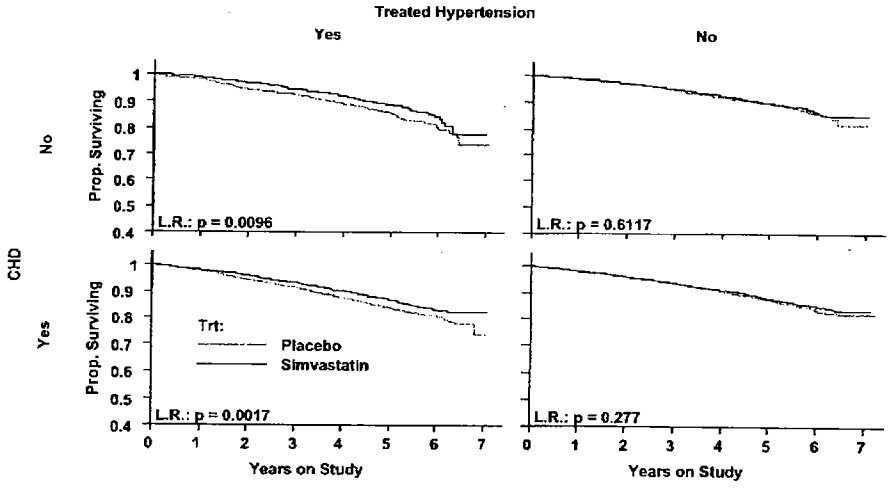
| | Simvastatin | Placebo |
|---|---|---|
| CHD | | |
| Taking ACE | 225/1289 (17.5%) | 239/1295 (18.5%) |
| Not taking ACE | 492/5405 (9.1%) | 688/5397 (12.7%) |
| Non-CHD | | |
| Taking ACE | 39/700 (5.6%) | 57/695 (8.2%) |
| Not taking ACE | 142/2875 (4.9%) | 228/2880 (7.9%) |

Figure 14. Kaplan-Meier curves for MCE by CHD and ACE inhibitor use




The absence of a significant reduction in deaths among patients presenting without treated hypertension was surprising given the size of the group (~12,000 patients). Looking at the total mortality data by presence/absence of CHD shows that essentially no effect is seen for patients without hypertension regardless of CHD disease (Figure 15). The results on CHD mortality were similar with non-significant results (p=0.06) seen for non-hypertensives.

Figure 15. Kaplan-Meier curves for total mortality by treated hypertension and CHD



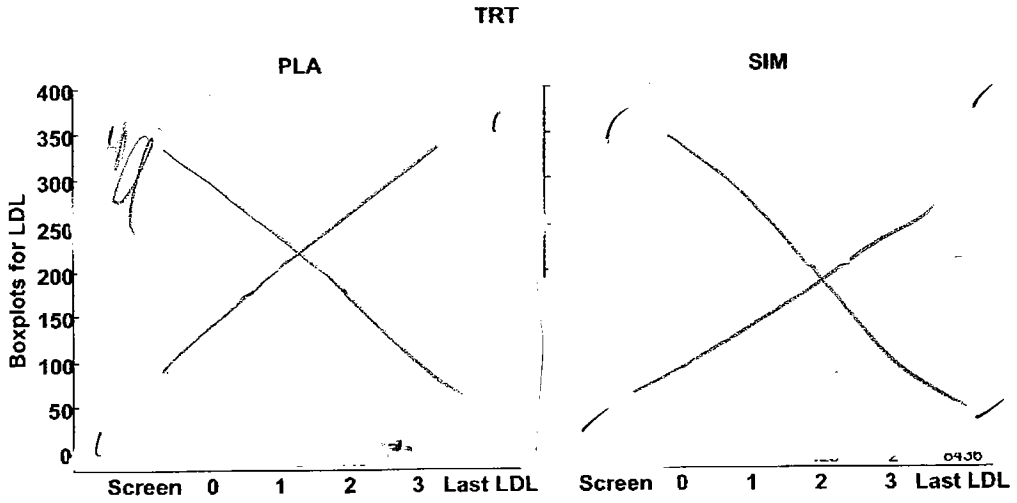
12. Relationship of LDL-C and outcome

Unlike previous large statin trials, there were no entry criteria regarding LDL-C levels in HPS, though a total cholesterol of greater than 130 was required. So patients at risk of CHD had a range of LDL-C values at screening (Figure 16); about 17% had LDL-C less than 100 and the median was about 130 mg/dL.

According to the study report, follow-up lipid profiles were done during a selected period of about 2 weeks each year in each clinic for about 1,000 total patients who were scheduled for a follow-up visit. These samples were taken four or five times (both numbers are mentioned in the study report) before 9/2000. A final sample on all patients remaining on study were taken between 9/2000 and 3/2001. Appendix 3 shows the distribution of the data at each visit and the number of patients measured. (Note that the data is portrayed in the appendix by visit, not calendar time, so there are not necessarily 1,000 patients for each exposure year). Non-fasting lipid samples were measured by direct assay (about 5% lower than indirect method).

There were not sufficient numbers of patients with repeated LDL-C measures on study to get an estimate of how LDL-C changes over time. The figure below illustrates two points about the data: 1) about 80% of the patients had an LDL-C measurement during the double-blind treatment period and 2) less than 20% of the patients had more than one LDL-C measurement on trial.

Figure 16. Boxplots of LDL-C by treatment




Numbers under box are sample sizes. Label 0 refers to the allocation visit, 1 refers to first LDL-C for patients having more than one LDL-C while on assigned treatment; 2 refers to second LDL-C for patients having more than two LDL-C's while on assigned treatment; 3 refers to third LDL-C for patients having more than three LDL-C's while on assigned treatment and last LDL-C is either the only LDL-C measured for a patient or the last one measured for patients with multiple measurements.

LDL-C means at screening and at the allocation visit are the same for both treatment groups with mean decreases of 41% seen during the run-in period in both groups (Table 24). Half the patients in both groups had LDL percent decreases greater than 43%.

This reviewer thinks the applicant's plots in the study report (Figures 17-22 in Section 7.4), Figure 2 in their European Heart Journal publication and Table 2 in their Lancet publication are misleading because these depictions of the data imply that the same group of patients were followed for the duration of the trial. Comments regarding changes in response over time seem inappropriate for the data depicted.

To get a sense of the change in LDL-C, this reviewer summarized the LDL-C data for those patients who had data during each phase of the trial (Table 24). These data show again the comparability of response at screening, run-in and allocation for the two treatment groups. At study end, simvastatin patients show a mean decrease of 29% from their original screening value; about 38% of the patients had a decrease of 40% or greater. These LDL-C responses are consistent with the LDL-C responses reported in the simvastatin label.

Table 24. LDL-C during the trial for all patients and for patients with data at each treatment phase (Means and standard deviations)

| | Simvastatin | Placebo |
|---|---|---|
| **LDL-C results (mg/dL) based on all available data at screening and end of run-in** | | |
| | (n=10,269) | (n=10,267) |
| Screening LDL mg/dL | 130.6 (32.0) | 130.6 (31.9) |
| | (n=10,264) | (n=10,264) |
| Run-in LDL mg/dL | 76.5 (25.4) | 76.7 (25.1) |
| Change | -54.1 (24.9) | -53.9 (24.9) |
| % change | -40.9% (15.6) | -40.7% (15.4) |
| **LDL-C results (mg/dL) for patients with complete data** | | |
| | (n=8,432) | (n=8,184) |
| Screening LDL mg/dL | 130.4 (31.8) | 130.2 (31.5) |
| Run-in LDL mg/dL | 75.9 (24.7) | 76.1 (24.4) |
| % change | -41.3% (15) | -41% (15.2) |
| Study End LDL mg/dL | 90.4 (31.3) | 123.1 (33.7) |
| % change screening to end | | |
| Mean | -29% (23) | -2% (27) |
| Median | -35% | -1.5% |

Note that run-in values were measured at the end of the run-in period after 6 weeks of treatment with simvastatin.

Percent change and absolute change of LDL-C were related to the screening LDL-C as shown in Table 25 and were essentially the same for both groups. These numbers illustrate that a range of LDL-C responders were recruited in this study.

Table 25. % change in LDL-C during the run-in period by screening LDL-C for both treatment groups

| Screening LDL-C mg/dL (quintiles) | Simvastatin | Placebo |
|---|---|---|
| <103 | (n=1998) | (n=2001) |
| Change | -33 | -32 |
| % Change | -37% | -36% |
| 103 to <121 | (n=2062) | (n=2035) |
| Change | -45 | -45 |
| % Change | -40% | -40% |
| 121 to <136 | (n=1963) | (n=1964) |
| Change | -53 | -53 |
| % Change | -41% | -41.5% |
| 136 to <156 | (n=2156) | (n=2188) |
| Change | -62 | -61 |
| % Change | -42% | -42% |
| 156 or greater | (n=2085) | (n=2076) |
| Change | -76 | -76 |
| % Change | -43% | -43% |

One of the objectives of HPS was to show that simvastatin was effective regardless of lipid levels. (It is worth recalling that LDL measurements are at screening, before the run-in. This reviewer found that the screening values for the placebo patients do not necessarily match their values after stopping run-in simvastatin and switching to placebo.) Since qualifying disease is an important factor, this reviewer looked at four groups of patients defined by the qualifying disease by screening LDL-C level. Figure 17 shows that patients with LDL-C under 100 (for both treatment groups) are comprised of a higher percentage of diabetics while the other LDL-C groups have a higher percentage of CHD alone patients. It is unlikely that this difference would bias interpretation of the subgroup effects.

Figure 17. Percentage of patients by qualifying disease and screening LDL-C

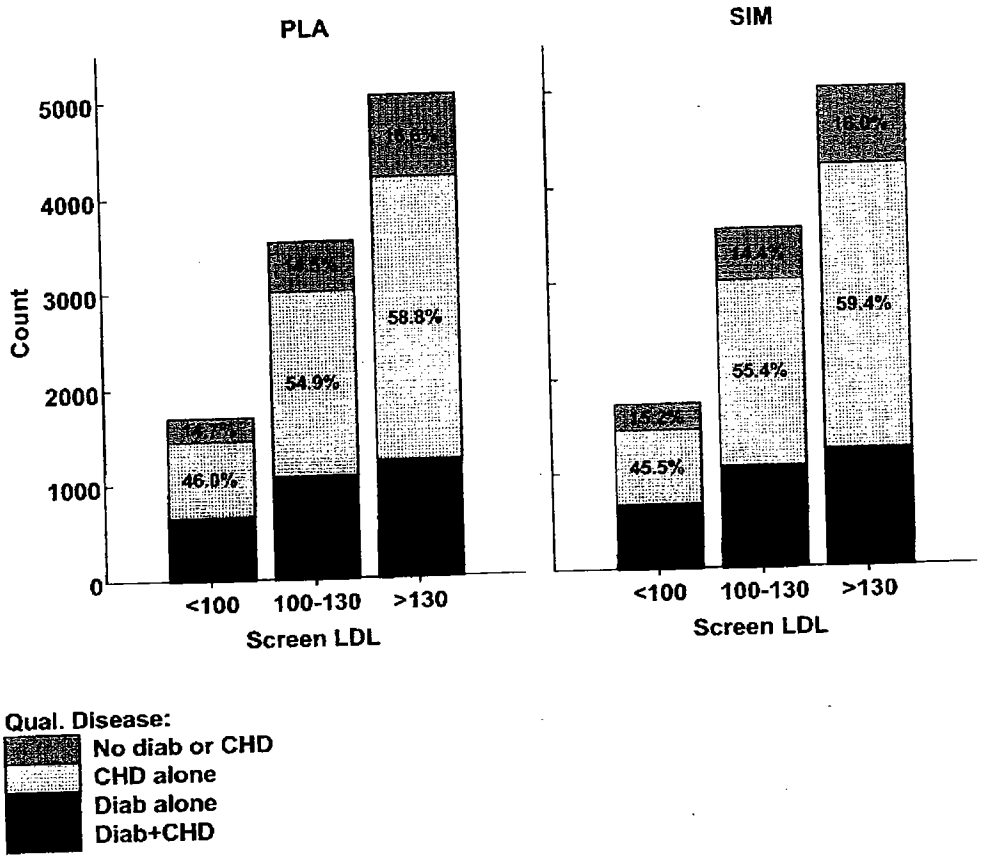
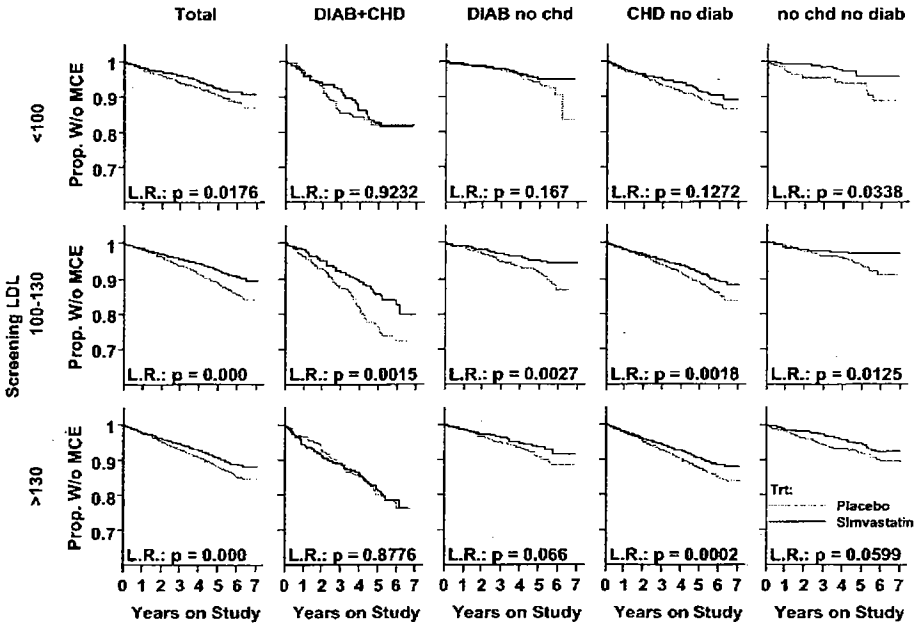



Figure 18 on the following page illustrates the response on MCE for the groups depicted in the bar chart on the previous page. Subsetting on two factors with multiple levels (disease and LDL-C) can produce small numbers; particularly for patients with LDL-C<100 (17% of the HPS

population) and patients with diabetes and CHD (about 10% of the HPS population). This reviewer, though, would argue that it is necessary to look further, particularly, at the LDL-C<100 groups

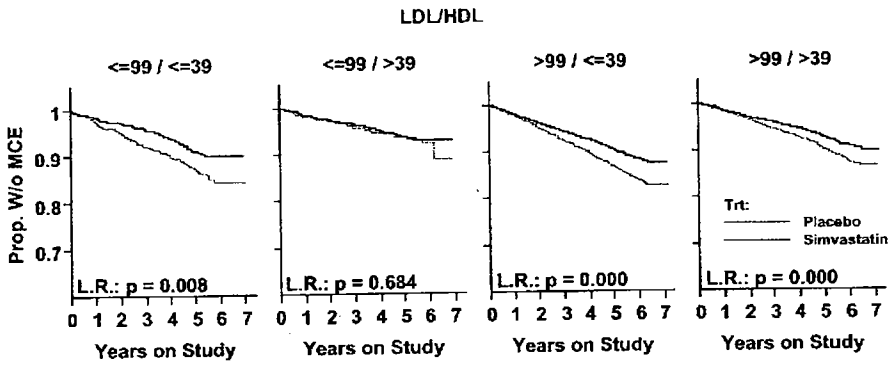
The first column of Figure 18 shows the effects on MCE for all patients for each of the three screening LDL-C categories (<100, 100-130 and >130, protocol-defined groups); significant results are seen at each of the LDL-C levels. Looking to the disease subgroups, in general the results for patients with LDL-C<100 are not as convincing as the results for the patients with LDL-C>100 though the comparisons tend to trend in favor of simvastatin.

Figure 18. Survival curves by screening LDL-C group for MCE (y-axis starting at 0.6)




This reviewer also looked at LDL-C with HDL-C and Apo A1. Figure 19 on the following page illustrates the MCE results subsetting on both LDL-C and HDL-C. An LDL-C cutoff of 100 mg/dL and the median for HDL-C were used to define the groups; additionally this reviewer used cutpoints for LDL-C up 115 to boost the sample size and observed that the results were not sensitive to the cutpoint of 100. No significant treatment effect is observed for patients with low LDL and high HDL (second graph). Results for Apo A1 were similar and are not shown here.

Figure 19. MCE by screening LDL-C and screening HDL-C (y-axis starting at 0.6)




To examine this issue further this reviewer looked at the results for the two subgroups depicted in the two graphs to the left above (LDL-C<100+HDL-C≤39 and LDL-C<100+HDL-C>39) for other endpoints. It is worth noting that that sample sizes for these two groups are both small by the standard of HPS (less than 1,000 patients in each treatment group). The placebo rates in Table 26 illustrate the difference in risk between the subgroups with patients with lower HDL-C clearly at higher risk on all endpoints except stroke. (This could be due to the one difference between the groups this reviewer found; the group with low HDL-C is 89% male while the group with high HDL-C is 71% male.) The lack of treatment effect seen for MCE in the low LDL-C, high HDL-C group is due to the unfavorable results seen for CHD mortality. Note in the subgroup with low LDL-C, low HDL-C, the MCE results strongly favor simvastatin over placebo (p<.004). Benefit on MVE is seen in both subgroups albeit for different reasons while the MCE results are inconsistent. Larger sample sizes would be required to confirm these results.

Table 26. Endpoint results for patients with LDL-C less than 100 and HDL-C above and below 39 (the median for the overall population)

| | Simvastatin | Placebo | RR | 95% CI | P-value |
|---|---|---|---|---|---|
| LDL-C<100+HDL-C>=39 | n=922 | n=924 | | | |
| Total Mortality | 114 (12.4%) | 118 (12.8%) | 0.97 | 0.75, 1.25 | .80 |
| CHD Mortality | 48 (5.2%) | 40 (4.3%) | 1.20 | 0.79, 1.83 | .39 |
| NFMI | 14 (1.5%) | 30 (3.2%) | 0.47 | 0.25, 0.88 | .02 |
| **MCE** | **60 (6.5%)** | **63 (6.8%)** | **0.95** | **0.67, 1.35** | **.77** |
| **MVE** | **127 (13.8%)** | **158 (17.1%)** | **0.79** | **0.62, 1.00** | **.05** |
| Procedures | 48 (5.2%) | 61 (6.6%) | 0.79 | 0.54, 1.15 | .21 |
| Stroke | 30 (3.3%) | 51 (5.5%) | 0.58 | 0.37, 0.91 | .02 |
| LDL-C<100+HDL-C<39 | n=798 | n=777 | | | |
| Total Mortality | 109 (13.7%) | 122 (15.7%) | 0.87 | 0.67, 1.13 | .30 |
| CHD Mortality | 49 (6.1%) | 59 (7.6%) | 0.81 | 0.56, 1.18 | .28 |
| NFMI | 25 (3.1%) | 45 (5.8%) | 0.53 | 0.33, 0.86 | .01 |
| **MCE** | **69 (8.7%)** | **103 (13.3%)** | **0.64** | **0.47, 0.87** | **.004** |
| **MVE** | **155 (19.4%)** | **200 (25.7%)** | **0.74** | **0.60, 0.91** | **.004** |
| Procedures | 70 (8.8%) | 88 (11.3%) | 0.77 | 0.56, 1.05 | .096 |
| Stroke | 39 (4.9%) | 41 (5.3%) | 0.73 | 0.60, 1.44 | .73 |

To examine more carefully the upper ranges of LDL-C, this reviewer looked at the MCE and MVE results by screening LDL-C quintiles. For MCE, the results in the highest quintile are not statistically significant ($p<.10$) while they are significant for MVE (Figures 20 and 21). Higher doses may be warranted for patients presenting with high LDL-C.

Figure 20. MCE by screening LDL-C quintiles (y-axis starting at 0.6)

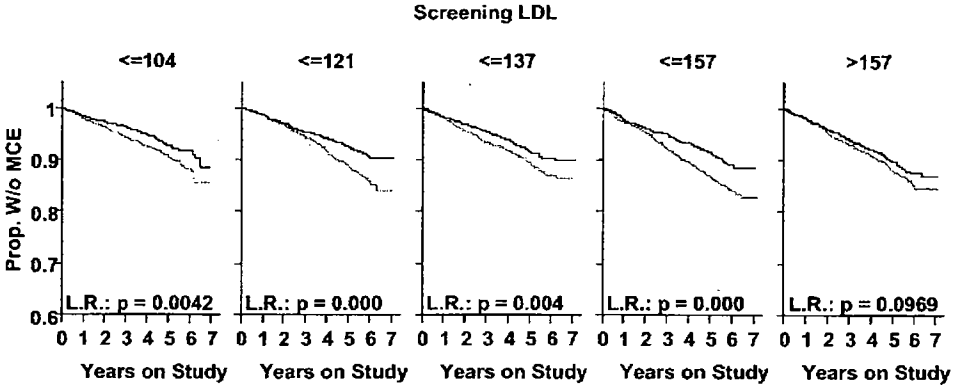
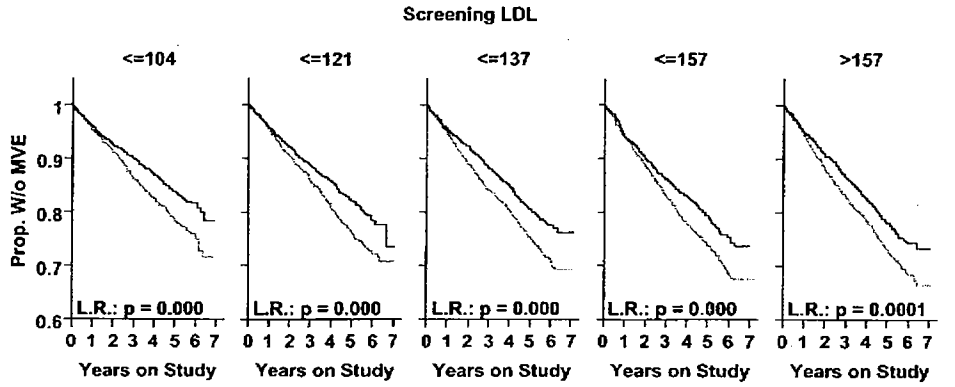
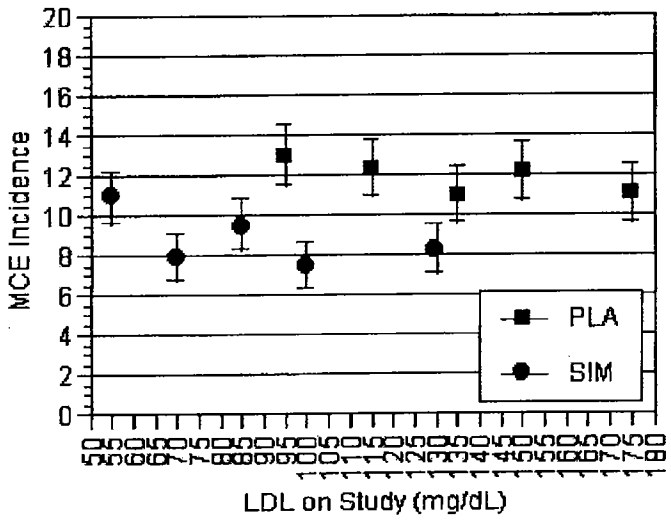



Figure 21. MVE by screening LDL-C quintiles (y-axis starting at 0.6)



To look at the relationship between on-treatment LDL-C[2] and MCE incidence in HPS, this reviewer computed incidences by LDL-C quintile for each treatment group. These incidences are plotted against the median of the LDL-C quintile range (Figure 22). This depiction of the data is similar to an analysis of 4S data reported by Pedersen et al (Circulation 1998;97:1453-1460) and to an analysis done for the FDA review of AFCAPS. The 4S and AFCAPS plots showed that the incidence of primary events was slightly graded over the observed range of LDL-C with rates in both groups increasing with LDL-C. Quite the contrary is seen in HPS where actually higher MCE incidences are seen for each treatment group at the lowest LDL-C quintile. This pattern of response may be related to the selection of the population where all patients were considered high risk regardless of their LDL-C level; although this pattern is not seen when looking at incidences by screening LDL-C only. It also may be an artifact due to the sporadic sampling for LDL-C.

Figure 22. MCE incidence by on-treatment LDL-C quintiles. Incidences are plotted against the median of the quintile.




13. Number needed to treat (NNT)

The number needed to treat (NNT) refers to the number needed to treat for a given length of time (trial duration) to prevent a single event. NNT is useful for comparing across trials because it reflects the placebo risk as well as the benefit. Table 27 shows NNT for five large lipid trials and HPS using a common composite endpoint comprised of NFMI and CHD mortality (MCE in

[2] On-treatment LDL was the LDL measured last on study. If this value was missing, the allocation visit LDL was used for the simvastatin patients and the screening visit LDL for the placebo patients. Also for placebo patients who were switched to a statin, their screening value was used.

HPS). The duration for all the trials was about 5 years with the exception of LIPID which was a 6-year study. The numbers for the five large trials were extracted from Table 2 in a publication by P. Moriarty (Using Both "Relative Risk Reduction" and "Number Needed to Treat" in Evaluating Primary and Secondary Clinical Trials of Lipid Reduction, The American Journal of Cardiology Vol 87, 2001, p 1206-1208).

The NNT illustrates the difference between treating a primary prevention population (AFCAPS, WOSCOPS and HPS patients without CHD; lightly shaded areas of the table) and a secondary prevention population (CARE, LIPID, 4S and HPS CHD patients; darkly shaded area of the table) with more patients needed to be treated to reap a benefit in a primary prevention population than in a secondary prevention population when the risk reductions are similar.

HPS enrolled a heterogeneous population of patients with and without a history of CHD or MI. In HPS, generally lower risk reductions are seen in higher risk groups (MI and other CHD patients) yielding similar NNT (30) to CARE and LIPID (33 and 28, respectively). It is interesting to note that the risk reductions in 4S and HPS are similar yet the number needed to treat in HPS is 3 times that in 4S; this of course reflects the difference in event rates. The event rates in the primary prevention populations of HPS are higher than the rates observed in AFCAPS and WOSCOPS and so the NNT's are lower than in those studies. Note that no population in HPS is actually a "true" low risk population since all patients were considered at high risk for a CHD event within five years of study entry.

Table 27. NFMI or CHD Mortality (MCE in HPS)

| | Placebo Rate | Relative Risk Reduction | NNT |
|---|---|---|---|
| AFCAPS | 5.5 % | 37% | 49 |
| WOSCOPS | 7.9% | 30% | 42 |
| CARE | 13.2% | 23% | 33 |
| LIPID | 15.9% | 23% | 28 |
| 4S | 28% | 31% | 11 |
| | | | |
| HPS | 11.8% | 27% | 32 |
| Diabetics w/oCHD | 8.4% | 36% | 34 |
| CVD/PVD w/o CHD | 9.2% | 33% | 33 |
| Pre-MI | 16.0% | 22% | 30 |
| CHD (MI+other) | 13.9% | 24% | 30 |
| | | | |
| Screening LDL-C<br><100<br>≥100 | <br>9.8%<br>12.2% | <br>24%<br>26% | <br>44<br>31 |

The NNT's computed based on screening LDL-C show that, though the risk reductions are similar the NNT differ by 13. So again in a population with a low risk (i.e. lower placebo rate), more patients need to be treated to show benefit for one patient.

# VII. Integrated Review of Safety

## A. Brief Statement of Conclusions

1. The incidence of total and CHD mortality was lower in patients on simvastatin compared to placebo independent of prior qualifying disease (i.e. MI, other CHD, nonCHD atherosclerosis or diabetes). The relative risk reduction for CHD mortality associated with simvastatin therapy was statistically significant in both sexes, whereas the risk reduction for total mortality was significant in males only.

2. There was a greater incidence of musculoskeletal adverse events, including CK elevations >10xULN, discontinuations for muscle enzyme elevations, and rhabdomyolysis/serious myopathy in patients on simvastatin compared to placebo but these rates were quite low (<0.1%).

3. There was one possible case of drug-related liver failure and more patients experienced multiple ALT elevations >3xULN on the simvastatin group compared to placebo but the incidence was quite low (<0.3%). There was no evidence that frequent liver function monitoring without clinical evidence of liver disease was helpful in preventing serious drug-related liver disease.

4. There was no clear association between neurological adverse events or cancer and the chronic use of simvastatin in this trial.

## B. Description of Patient Exposure

Similar numbers of patients were followed on simvastatin and placebo except that starting at about 8 months and more clearly visible by 18 months the drop off in patients in the placebo group is slightly greater reflecting the increase in mortality in this group. The mean follow up time was 5.3 years and the drop off in patients in both groups after 60 months reflects the end of the scheduled visits as the trial was drawn to a close.

Table 28
Number of Surviving Patients at Each Scheduled Follow-Up Visit Time Point

| Follow-Up (Months)† | Simvastatin Comparison | | | |
|---|---|---|---|---|
| | Active N=10269 | % | Placebo N=10267 | % |
| 4 | 10,233 | 99.6 | 10,231 | 99.6 |
| 8 | 10,176 | 99.1 | 10,158 | 98.9 |
| 12 | 10,107 | 98.4 | 10,088 | 98.3 |
| 18 | 10,016 | 97.5 | 9969 | 97.1 |
| 24 | 9909 | 96.5 | 9826 | 95.7 |
| 30 | 9794 | 95.4 | 9710 | 94.5 |
| 36 | 9664 | 94.1 | 9563 | 93.1 |
| 42 | 9521 | 92.7 | 9403 | 91.6 |
| 48 | 9389 | 91.4 | 9241 | 90.0 |
| 54 | 9193 | 89.5 | 9034 | 88.0 |
| 60 | 7370 | 71.8 | 7225 | 70.4 |
| 66 | 4947 | 48.2 | 4880 | 47.5 |
| 72 | 2347 | 22.9 | 2308 | 22.5 |
| 78 | 787 | 7.7 | 763 | 7.4 |
| 84 | 96 | 9.3 | 88 | 8.6 |

† The number of patients at each time point indicated represents the number of patients surviving up to that scheduled follow-up visit. It does not take clinic attendance into account.. Data Source: [4.1.7] Table 31 from P102.pdf

Compliance, determined as taking 80% or greater of the allocated medication during tablet counts, ranged from 94% at 4 months to 79% by 60 months in patients taking simvastatin and from 94% at 4 months to 72% by 60 months in patients taking vitamins. Non-compliance, determined as taking less than 10% of the allocated medication during tablet counts, ranged from 2% at 4 months to 19% by 60 months in patients on simvastatin and from 2% at 4 months to 26% by 60 months in patients taking vitamins.

## C. Methods and Specific Findings of Safety Review

### 1. TOTAL MORTALITY/CHD MORTALITY-

Total and CHD mortality were primary endpoints in this study and so were discussed in more detail in the Integrated Review of Efficacy. To briefly summarize, there was a 13% relative risk reduction in total mortality (12.9% vs. 14.7%, p=0.0003) and an 18% relative risk reduction in CHD mortality (5.7% vs. 6.9%, p=0.0005) in patients on simvastatin compared to placebo. There was also a trend for lower Non-CHD mortality between the simvastatin group (7.4%) compared to placebo (7.9%, p=0.10) but it was not statistically significant. Risk reductions in total and CHD mortality while on simvastatin therapy were seen in patients independent of the following baseline characteristics (i.e. MI, history of other CHD, nonCHD, atherosclerosis and diabetes). The relative risk reduction for CHD mortality associated with simvastatin treatment was statistically significant in both males and females, whereas the risk reduction for total mortality was significant in males only.

### 2. SERIOUS ADVERSE EVENTS/DISCONTINUATIONS-

Nonserious adverse events were not captured. Out of the 38,114 serious events observed in 6,486 patients on simvastatin (63%) and 6,765 patients on placebo (66%) only 16 were considered drug related. These included one case of liver failure on simvastatin and one case of hepatitis unspecified on placebo and 9 cases of myositis/myopathy, 6 on simvastatin and 3 on placebo.

Six patients discontinued medications because of liver enzyme elevations; all 6 were on simvastatin. Similarly, discontinuation of medications as a result of muscle enzyme elevations occurred in 6 patients receiving simvastatin whereas no placebo-treated patients required discontinuation for CK elevations. Muscle symptoms were frequently reported and occurred at similar rates on simvastatin and placebo suggesting that muscle symptoms alone (without CK elevations) are not good indicators for drug related events. Only one out of the 99 patients with discontinuation for muscle symptoms had a CK> 5xULN (CK=3,717, 14.9xULN) and that patient was on simvastatin.

**Table 29**
**Discontinuations Due to Serious Adverse Events in HPS**

| | Simvastatin N=10,269 | | Placebo N=10,267 | |
|---|---|---|---|---|
| | N | % | N | % |
| **Liver enzyme elevations** | 6 | 0.06 | 0 | 0 |
| **Muscle enzyme elevations** | 6 | 0.06 | 0 | 0 |
| **Muscle symptoms** | 49 | 0.48 | 50 | 0.49 |
| **Other symptoms** | 411 | 4.0 | 465 | 4.5 |
| **Other reasons** | 507 | 4.9 | 694 | 6.8 |

(data from AE.xpt dataset).

In summary, whereas there is a higher frequency of serious adverse events associated with muscle and liver enzyme elevations leading to discontinuations in therapy in patients on simvastatin compared to placebo, the overall incidence is quite small.

## 3. MUSCULOSKELETAL –RELATED ADVERSE EVENTS

CK ELEVATIONS
CK elevations have been widely used to screen for potential myotoxicity associated with statins.

CK measurements were not routinely done at follow up visits unless patients had muscle symptoms or Early Recall Visits. Out of the 1638 Early Recall Visits, most were in the simvastatin group 904 (55%) compared to placebo 734 (45%). Since mild CK elevations due to exercise or strenuous physical activity can typically resolve without any serious complications and without the need to discontinue therapy, it is more useful to compare large CK elevations > 5 or 10xULN and CK elevations associated with increases in ALT or myopathy when looking for a potential myopathic signal. Such situations are more likely to be associated with greater tissue damage and more serious complications.

**Table 30**
**The Number of Patients with CK Elevations on Simvastatin and Placebo in the HPS Dataset[1]**

| | Simvastatin | | Placebo | |
|---|---|---|---|---|
| **CK elevations** | **N** | **%** | **N** | **%** |
| CK>5xULN | 18 | 0.18 | 10 | 0.10 |
| CK>10xULN | 5 | 0.05 | 3 | 0.03 |
| **CK elevations associated with Alt>2xULN[2]** | | | | |
| CK>5xULN | 9 | 0.09 | 0 | 0 |
| CK>10xULN | 5 | 0.05 | 0 | 0 |
| **CK elevations in pts with muscle symptoms[3]** | | | | |
| CK>5xULN | 10 | 0.10 | 5 | 0.05 |
| CK>10xULN | 4 | 0.04 | 1 | 0.005 |
| **CK elevations associated with AE of myositis/myopathy[4]** | | | | |
| CK>5xULN | 3 | 0.03 | 1 | 0.005 |
| CK>10xULN (myopathy) | 3 | 0.03 | 1 | 0.005 |

[1]Data derived from 9/23/02 SAS dataset LABCK, LABALT[2], QMS[3], and AE[4]
The HPS dataset does not include most data from hospitalizations; it only includes data on 3 out of 9 patients on simvastatin and 1 out of 3 patients on placebo with CK>10xULN during hospitalizations. (Table 35, section 8.2 of applicant's submission)

There is clearly a higher incidence of CK elevations in patients on simvastatin compared to placebo especially in patients with ALT elevations or muscle symptoms. The overall incidence in patients is still quite small.

MYOPATHY AND RHABDOMYOLYSIS-
The diagnosis of myopathy is typically defined as CK>10xULN associated with unexplained muscle symptoms or weakness. However, the diagnosis of rhabdomyolysis has been less clearly

defined and is usually a clinical diagnosis. In their analysis the applicant used the cut off of CK>40xULN (e.g. 10,000U/L for an ULN of 250U/L) to identify rhabdomyolysis. This definition is likely to underestimate the number of cases as peak CK values can be missed during the course of the illness and therefore rhabdomyolysis has been reported with CK levels below 1000 U/L (Omar et. al 2001).

Most of the cases of rhabdomyolysis reported by the applicant were not picked up in the analysis of the CK elevations (see Table 30 above) reported in the LABCK dataset because the peak CK elevations occurred during hospitalizations. In fact only 2 out of the 8 cases of rhabdo/myopathy had CK>5xULN in the HPS CK dataset. This also means that the number of patients with CK elevations in Table 30 above was underestimated.

There is also a discrepancy between the definitions of myopathy and rhabdomyolysis used by the applicant and those used in the Lancet publication resulting in different reporting rates (see Table 31).

**Table 31**
**Number of Patients with Myopathy or Rhabdomyolysis**

| | Simvastatin | | Placebo | |
|---|---|---|---|---|
| **APPLICANT'S ANALYSIS**[1] | **N** | **%** | **N** | **%** |
| **Myopathy** (CK>10xULN) | 9 | 0.09 | 3 | 0.03 |
| **Rhabdomyolysis** (CK>10,000) | 4 | 0.04 | 1 | 0.01 |
| **LANCET PUBLICATION**[2] | | | | |
| **Myopathy** (No Rhabdo) | 5 | 0.05 | 1 | 0.01 |
| **Rhabdomyolysis** (CK>40xULN) | 5 | 0.05 | 3 | 0.03 |

[1]Data taken from applicant's submission Section 8.2.4 Table 34
[2]Data taken from Table 4 The Lancet 7/6/02, Vol 360, pgs 7-22

In their 9/16/02 submission, the applicant describes these discrepancies as due to interpretation of cases that were complex and/or missing information. In order to identify serious cases of rhabdomyolysis/myopathy to better compare treatment groups this medical reviewer prefers to use the definition of 1) CK>10,000 and/or 2) hospitalization for myopathy (i.e. CK >10xULN and unexplained muscle symptoms). This should give a better estimate of the incidence of rhabdomyolysis and serious myopathy. Using this definition there were 8 cases of rhabdo/myopathy on simvastatin (0.08%) compared to 2 cases on placebo. Since one of these placebo patients was on cerivastatin there was only one placebo patient with rhabdo/myopathy not associated with statin use in this trial (0.01%). There is clearly a higher risk of rhabdo/myopathy on simvastatin compared to placebo but again the incidence is quite small. All patients recovered after medication was discontinued.

For reference the frequency of rhabdomyolysis in patients on cerivastatin in this study was 1/194=0.5% (1/154 on cerivastatin and placebo, 0/40 on cerivastatin and simvastatin). Although

this represents a small number of patients, the frequency of rhabdomyolysis was almost 10 times higher than seen with simvastatin in this study. This data is consistent with the observation that [redacted] is associated with a higher incidence of rhabdomyolysis/myopathy [redacted]

Four out of the 8 cases of rhabdo/myopathy observed in this study occurred in patients taking other drugs know to interact with simvastatin. Two patients were on erythromycin (2/12=17%), a potent inhibitor of cytochrome P-450 (CYP3A4), and two were on verapamil (2/202=1.0%), a CYP3A4 substrate. In contrast, no patients in the placebo group receiving concomitant erythromycin (n=16) or verapamil (n=169) experienced rhabdomyolysis/myopathy. The current approved labeling for simvastatin warns about the increased risk of myopathy with concomitant administration of erythromycin or verapamil (also see USE OF CONCOMITANT MEDICATIONS ASSOCIATED WITH MYOPATHY/RHABDOMYOLYSIS below).

One of the cases of rhabdo/myopathy occurred in a patient who was started on 20mg simvastatin in addition to the 40mg study simvastatin. This combined dose of 60mg is within the currently approved maximal daily dose of simvastatin (80mg). However, it is known that the incidence of myopathy/rhabdomyolysis is dose related with statins. The current label for Zocor estimates the incidence from clinical trials as 0.07% at 40mg and 0.3% at 80 mg.

One case of rhabdo/myopathy occurred in a 66y/o male with chronic renal failure. Patients with severe renal disease or creatinine > 2.3mg/dl (>2xULN) were excluded from the study. This patient had a creatinine measurement of 1.9mg/dL noted at screening. Higher systemic exposure has been reported in patients with severe renal insufficiency and the current label recommends starting patients with severe renal insufficiency on a daily dose of 5mg of simvastatin.

USE OF CONCOMITANT MEDICATIONS ASSOCIATED WITH MYOPATHY/RHABDOMYOLYSIS

The current Zocor label warns against concomitant therapy with potent inhibitors of CYP3A4 including itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors-(amprenavir, indinavir, saquinavir, lopinavir, ritonavir, nelfinavir), nefazodone, or large quantities of grapefruit juice. It also warns that there may be an increased risk of myopathy with verapamil compared to other calcium channel blockers.

The current Zocor label warns that patients should not exceed 10mg/day of simvastatin in combination with cyclosporin, fibrates and niacin. In this study concurrent use of cyclosporin, fibrates or high dose niacin were exclusion criteria. And patients with a condition likely to result in organ transplantation and the need of cyclosporin were also excluded.

Despite these warnings a small number of patients were placed on potentially toxic drug combinations during the study.

| Table 32 Concomitant Drug Use With Medications Associated With Myopathy/Rhabdomyolysis | | | |
|---|---|---|---|
| **Drug** | **Simvastatin (number of patients)** | **Placebo (number of patients)** | **Rhabdomyolysis (number of patients, % on Simvastatin)** |
| itraconazole | 1 | 0 | 0 |
| ketoconazole | 1 | 0 | 0 |
| erythromycin | 12 | 16 | 2 (2/12=17%) |
| clarithromycin | 6 | 5 | 0 |
| HIV protease inhibitors | 0 | 0 | 0 |
| nefazodone | 2 | 3 | 0 |
| cyclosporin | 0 | 3 | 0 |
| gemfibrozil | 0 | 0 | 0 |
| fenofibrate | 0 | 0 | 0 |
| niacin | 0 | 0 | 0 |
| verapamil | 202 | 169 | 2 (2/202=1.0%) |

The overall incidence of rhabdomyolysis was 4/224=2% in patients given 40mg simvastatin and one of these potentially interacting medications; much higher than the background incidence reported in clinical trials with 40mg of simvastatin alone (0.07%).

LDL-C and CK ELEVATIONS/RHABDOMYOLYSIS

In order to see if there was an association between low LDL-C on simvastatin during the run-in period and the development of CK elevations or rhabdomyolysis, the distribution of LDL-C in these populations was analyzed.

| Table 33 LDL-C (mg/dL) after Run-In Period | | | |
|---|---|---|---|
| | **Patients with Rhabdo[1]** (n=6) | **Patients with CK>5x on Simvastatin** (n=18) | **Patients allocated to Simvastatin** (n=10,264) |
| **Max** | 91 | 126 | 263 |
| **75%** | 81 | 90 | 90 |
| **Median** | 57 | 59 | 73 |
| **25%** | 51 | 48 | 59 |
| **Min** | 43 | 41 | 12 |
| **Upper 95% mean** | 82 | 81 | 77 |
| Mean | 63 | 69 | 76.5 |
| Lower 95% mean | 45 | 56 | 76 |

[1]Two patients had rhabdo during run in-period and were not continued in the trial so LDL-C data is not available.

There is a trend with lower mean and median LDL-C levels in patients on simvastatin who developed rhabdomyolysis or had CK elevations later on during the study. But the number of patients with adverse events is low and the variation wide so the 95% upper limit of the mean, 82 and 81mg/dL for patients on simvastatin with rhabdomyolysis or CK >5xULN respectively, lie above the mean for all patients on simvastatin i.e.76.5mg/dL. Or another way of looking at the data is that almost 1300 patients with LDL-C below 50mg/dl during the run-in who were later allocated to the simvastatin treatment group did not develop rhabdomyolysis or large CK elevations (>5xULN) during the 5 year trial.

Since LDL-C measurements were not performed routinely during the study, it is also not known if the LDL-C levels may have dropped more severely prior to the development of the myopathic adverse events. In conclusion, whereas LDL-C levels appear somewhat lower in patients who go on to develop rhabdomyolysis, it is not known if monitoring LDL-C levels during ongoing therapy would decrease the likelihood of these events.

STUDY DESIGN-
Whereas the overall incidence of CK elevations, myopathy and rhabdomyolysis was low in this study, the actual incidence may have been underestimated because of the unique study design used in this trial. All patients were exposed to a six week course of the active drug during the run-in period and this information was used to select out patients prior to allocation to treatment groups in this trial.

1) Patients with baseline elevations in CK (78), LFTs (656) or creatinine (192) were excluded from the study.

2) Patients exposed to the 6 week course of simvastatin during the run-in period dropped out prior to allocation because of the following potentially drug-related reasons:

New unexplained muscle pain (531)
Unwell possible side effects (4)
Muscle symptoms (61)
Non-specific symptoms (87)

The total number of patients here is small 1,609/20,536=7.8% in relation to the total number of patients followed in this trial. But it is possible that patients with a higher tendency to develop significant muscle toxicity may have been culled from the trial. In addition a much larger group of patients equal to 15% of the number of patients allocated (3,126/20,536=15%) gave no reason for why they did not attend the allocation visit. It is possible that they too may have decided not to enroll in the study because of some unreported adverse event during the study run-in.

**4. LIVER-RELATED ADVERSE EVENTS**

LIVER TRANSAMINASE ELEVATIONS-
Liver transaminase elevations have been widely used to screen for potential hepatotoxicity associated with statins. Whereas ALT elevations have been associated with statins and appear to be dose related, the incidence of drug induced hepatitis and liver failure seen with statins is quite low.

ALT was measured at the screening visit prior to the run-in period, and before active treatment was started. Patients were not entered into the trial if ALT>1.5xULN or ALT>1≤1.5ULN and GGT, AST or ALP>2xULN, or GGT, AST, ALP>4xULN. 359 patients had an abnormal ALT, and 297 patients had other different liver function test abnormalities at the screening visit. So 656/32,415=2% of the patients entering the run-in period were not continued in the trial. ALT was measured at all visits. ALT values obtained during out of study hospitalizations were not included in the applicant's dataset. So out of 41 patients (20 on simvastatin and 21 on placebo) with diagnoses of hepatitis, chronic hepatitis, cirrhosis, liver biopsy, liver failure and liver problem unspecified during the course of the study only 6 had Alt elevations > 3xULN in the dataset (and only 16 had ALT> 1xULN). Therefore, the data in Table 34 is an underestimate the true incidence of LFT elevations in patients during this study.

**Table 34**

**ALT Elevations in patients taking Simvastatin[1]**

| | Simvastatin | | Placebo | | Ratio |
|---|---|---|---|---|---|
| **Single Elevation** | **N** | **%** | **N** | **%** | **Simvastatin/Placebo** |
| **≥3xULN** | 78 | 0.78 | 71 | 0.71 | 1.1 |
| **≥6xULN** | 16 | 0.16 | 15 | 0.15 | 1.1 |
| **≥9xULN** | 7 | 0.07 | 6 | 0.06 | 1.2 |
| **Multiple Elevations** | | | | | |
| **≥3xULN** | 24 | 0.24 | 13 | 0.13 | 1.8 |
| **≥6xULN** | 4 | 0.04 | 2 | 0.02 | 2.0 |
| **≥9xULN** | 3 | 0.03 | 1 | 0.01 | 3.0 |

[1]Data derived from 9/23/02 SAS dataset LABALT, visit number ≥0 were used.

There is overall a slightly higher frequency of multiple ALT elevations reported for patients on simvastatin (0.03 to 0.24%) compared to placebo (0.01 to 0.13%), but it is still much lower than the rate seen for other statins at the 40mg dose (0.3 to 1.5% for ALT >3xULN), and the rate seen for LFT abnormalities in patients during the screening visit (2%).

More patients were discontinued because of LFT abnormalities on simvastatin (N=57) compared to placebo (N=45). And slightly more patients with ALT >3xULN discontinued on simvastatin (N=47) compared to placebo (N=42). (Data obtained from LABALT>=135 and DISPOS dataset RDSUDY=Stopped study statin). Clearly about 40% of patients with ALT>3xULN were able to complete the study (simvastatin N=31, placebo N=29). These data suggest that ALT elevations are only slightly more frequent on simvastatin than placebo and not usually associated with progressive hepatic disease.

**Figure 23-Incidence of ALT >3xULN in Patients on Placebo over time (days)**

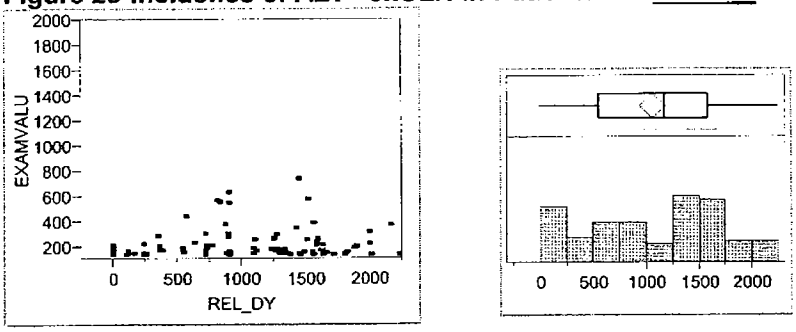
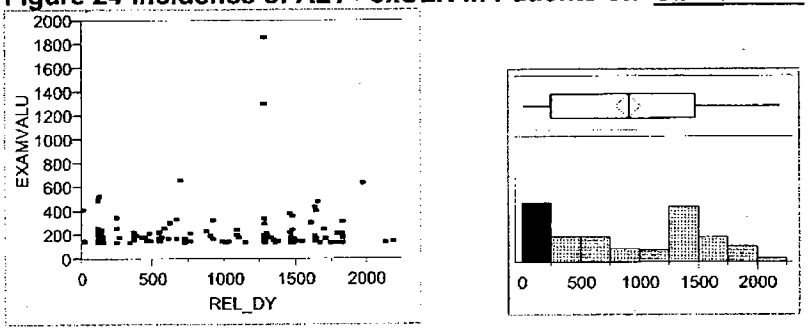



**Figure 24-Incidence of ALT >3xULN in Patients on Simvastatin over time (days)**




Whereas transaminase elevations >3xULN occurred slightly more frequently during the initial 250 days in patients on simvastatin and the maximum elevations seen on simvastatin were higher than observed on placebo, elevations continued through out the entire length of the trial in patients on both simvastatin and placebo. Suggesting that there is no optimum time for LFT monitoring.

Since 2% of the patients entering HPS run-in period did not proceed to treatment allocation because of abnormal LFTs at the screening visit it is not possible to know if there may have been at higher risk of liver disease if they had been included in the trial. Therefore, it is recommended that LFT monitoring continue to be performed before starting therapy with simvastatin. Without a placebo controlled trial to evaluate the safety of simvastatin in patients with liver disease, use of simvastatin should continue to be contraindicated in patients with active liver disease or unexplained persistent transaminase elevations as is currently described in the WARNINGS section of the Zocor label.

HEPATITIS/LIVER FAILURE

There were 41 patients with hepatic disease with out a clear etiology that could have been drug related. These were almost equally split between patients in the simvastatin group (20=0.2%) and

patients in the placebo group (21=0.21%). These included 10 cases of "unspecified hepatitis", one case of "chronic hepatitis", 16 cases of "cirrhosis/chronic liver disease", 8 cases of "liver biopsy", 2 cases of "liver failure" and 16 cases of "liver problem unspecified". A narrative was submitted for only one patient # 100826 who was hospitalized for 63 days on day 874 of the study with "hepatitis unspecified" and "liver failure". In this case the patient had been on simvastatin, the drug was stopped and the patient eventually recovered. The case was considered to be life-threatening with peak lab values of ALT >1000 IU/L (>20xULN), AST 1934 IU/L (47xULN) and bilirubin 30 mg/dL (30xULN).

Whereas the frequency of liver failure and hepatitis was rare in this trial questioning the necessity for routine liver function monitoring, it is still recommended that any patients with symptoms of liver disease be tested for liver transaminase elevations. Should an increase in AST or ALT of 3xULN or greater persist, the drug should be withdrawn as currently recommended in the Zocor label.

**5. NEURO-RELATED ADVERSE EVENTS**

There have been case reports of CNS effects such as neuropathy in patients on statins. There have also been reports suggesting that statins may be used to treat Alzheimer's. So the AE database supplied by the applicant was screened for neurological adverse events. There is no clear signal that exposure to simvastatin in this trial was related to an increase in neurologic events (see Table 35).

NEUROPATHY-

Despite an association with statins and the risk of polyneuropathy in case controlled trials (Backes and Howard 2003, Gaist et al 2002) there was no increase in the incidence of peripheral neuropathy over placebo rates in this trial, with 5 such patients on simvastatin and 5 on placebo. It is possible that cases of peripheral neuropathy could have been missed since the study was not designed to identify such patients but even using a more general definition of neuropathy and combining potential alternative diagnoses of adverse events that may be related to neuropathy there is still no difference in the incidence of these adverse events in the simvastatin group (N=35, 0.17%) compared to placebo (N=31, 0.15%, see Table 35). There was a slightly higher frequency of cranial nerve palsies in patients on simvastatin (5 vs. 2) but this was canceled out by a slightly higher incidence of motor neuron disease in patients on placebo (6 vs. 1). Dysfunction of certain cranial nerves, peripheral neuropathy and peripheral nerve palsy are already included in the ADVERSE EVENTS section of the Zocor label as having been reported in association with drugs in the statin class.

DEMENTIA-

There was a slightly higher frequency of cases of Alzheimer's disease or Alzheimer's type dementia in patients on simvastatin (N=6) compared to placebo (N=3). Since the total number of patients is small, it is hard to draw conclusions from these data but they call in to question whether simvastatin may be helpful in the treatment of Alzheimer's disease as had been previously speculated. When looking at all patients with potential diagnoses of dementia including Alzheimer's disease, confusion, disorientation, dementia or cognitive impairment,

there is no difference in the frequency of patients in the simvastatin group (N=35, 0.34%) compared to placebo (N=33, 0.32%).

A cognitive function questionnaire was added at the final follow-up visit. This includes information on 8086/10269=79% of the patients on simvastatin and 7834/10267=76% of the patients on placebo. No similar questionnaire was included at the allocation visit so it is not possible to compare individual patients scores in response to therapy, but it is possible to compare patients on simvastatin to placebo at the end of the study. According to the applicant, significantly impaired cognitive function, defined as a score of <22, was seen in a similar percentage of patients on simvastatin 23.6% and placebo 24.2% (Data taken from applicant's P102 Clinical Study Report Table 23 Section 7.3), suggesting that there was no gross impairment of cognitive function in patients on long term simvastatin therapy. Clearly this analysis would be unlikely to pick out subtle cognitive differences between the groups.

PSYCHOSIS

Whereas most CNS adverse events were well distributed between treatment groups, it seemed unusual that there were 6 cases of the composite group (hallucinations + schizophrenia + transient organic psychosis/ acute psychosis) in the simvastatin group and none on placebo. This included 3 cases of patients with hallucinations, 2 with transient organic psychosis and 1 with schizophrenia. I could not find any reference suggesting that statins can be associated with acute psychosis in the literature, however, the current Zocor label does include psychic disturbances in the ADVERSE EVENTS section as having been reported in association with drugs in the statin class.

Table 35

Total Numbers of Patients with Neurological Adverse Events[1]

| Category | REPTTERM | S | SV | V | - | S+SV/ V+ - |
|---|---|---|---|---|---|---|
| Dementia | alzheimers disease/alzheimers type dementia | 5 | 1 | 2 | 1 | 2.0 |
| | confusion or disorientation or confusion unspecified | 3 | 5 | 5 | 5 | 0.8 |
| | dementia/cognitive impairment | 13 | 8 | 15 | 5 | 1.1 |
| | Total for Dementia/Memory loss/Amnesia | 21 | 14 | 22 | 11 | 1.1 |
| Psychiatric | anxiety/ feeling tense/ panic attacks or stress/ stress-related problems | 2 | 2 | 4 | 2 | 0.7 |
| | attempted suicide or self-inflicted injury/deliberate overdose or self mutilating/ cutting/ stabbing | 9 | 6 | 3 | 8 | 1.4 |
| | depressed or depressive illness/depression or manic depressive/ bipolar affective or giddiness | 22 | 19 | 18 | 18 | 1.2 |
| | hallucinations or schizophrenia or transient organic psychosis/ acute psychosis | 5 | 1 | 0 | 0 | ∞ |
| | nervous breakdown | 4 | 2 | 5 | 0 | 1.2 |
| | psychological problem/ neurosis nos or psych assessment | 3 | 2 | 2 | 3 | 1.0 |

Table 35
Total Numbers of Patients with Neurological Adverse Events[1]

| Category | REPTTERM | S | SV | V | - | S+SV/ V+ - |
|---|---|---|---|---|---|---|
| | Total for Psychiatric Illnesses | 45 | 32 | 32 | 31 | 1.2 |
| Neuropathy | cranial nerve problem/palsy | 2 | 3 | 2 | 0 | 2.5 |
| | double vision/ diplopia | 4 | 1 | 4 | 2 | 0.8 |
| | motor neurone disease | 0 | 1 | 3 | 2 | 0.2 |
| | multiple sclerosis | 2 | 2 | 0 | 3 | 1.3 |
| | peripheral neuropathy/neuropathy nos | 2 | 3 | 3 | 2 | 1.0 |
| | trapped nerve/compressed nerve or neurologic pain/neuralgia or numbness or sensory symptoms | 9 | 2 | 4 | 5 | 1.2 |
| | weakness present - motor symptom/ specific parts of body | 3 | 1 | 1 | 0 | 4.0 |
| | Total Neuropathy or Possible Peripheral Nerve Involvement | 22 | 13 | 17 | 14 | 1.1 |
| Other | blackout/loss of consciousness/loc | 7 | 19 | 12 | 15 | 1.0 |
| | collapse | 44 | 44 | 62 | 52 | 0.8 |
| | dizziness (not vertigo) | 14 | 13 | 14 | 13 | 1.0 |
| | encephalitis | 1 | 1 | 0 | 1 | 2.0 |
| | epilepsy/fit or convulsion in known epileptic/new diagnosis | 13 | 16 | 10 | 13 | 1.3 |
| | faintness/ lightheadedness | 1 | 5 | 3 | 0 | 2.0 |
| | fall or accident unspecified | 23 | 37 | 33 | 33 | 0.9 |
| | fit/ convulsion unspecified (not known epilepsy) | 12 | 17 | 12 | 13 | 1.2 |
| | neurological investigations | 9 | 4 | 6 | 6 | 1.1 |
| | tremor | 1 | 1 | 0 | 0 | ∞ |
| | weakness | 1 | 1 | 2 | 0 | 1.0 |
| | Total Other (including Seizures and ?Central Neuro Deficits) | 126 | 158 | 154 | 146 | 1.1 |

[1]Data taken from AE dataset , S-simvastatin, SV-(simvastatin + vitamins), V-vitamins, - placebo

S+SV/ V+ - the ratio of $\frac{\text{simvastatin + (simvastatin + vitamins)}}{\text{vitamins + placebo}}$

**6. CANCER-RELATED ADVERSE EVENTS**

There is always concern about potential long term consequences of chronic therapy with any medication. This was highlighted in the CARE study with the unexpected finding of excess breast cancer cases in women randomized to treatment with pravastatin (12=4.2%) compared to placebo (1=0.3%). However, this finding was not reproduced in a follow up study, LIPID, which included more than twice as many women, where similar numbers of patients developed breast cancer on pravastatin (10=1.3%) as placebo (9=1.2%). In HPS there was no statistically significant difference between the simvastatin and placebo groups in the incidence of cancer at any individual site or at all combined sites. Specifically, looking at breast cancer rates there were fewer patients on simvastatin (38=1.5%) compared to placebo (52=2.0%) experiencing this event. Whereas not statistically significant the risk ratio was 0.73 with 95% CIs of (0.48-1.10)

showing a trend in favor of simvastatin. Comparing the cancer rates at individual sites from the applicants study report, breast cancer, in fact, showed the highest trend in favor of prevention with simvastatin, whereas non-melanoma skin cancer rates showed the highest trend in favor of prevention with placebo, 203=2.0% on placebo compared to 242=2.4% on simvastatin with a risk ratio of 1.18 and 95% CIs of (0.98-1.43).

There were also no statistically significant differences between use of vitamins and placebo in the incidence of cancer at any individual site or at all combined sites. The trend was greatest in favor of vitamins for preventing genitourinary cancer whereas it was greatest for placebo for preventing respiratory cancers. This later finding is interesting in light of studies like the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study which showed that beta-carotene modestly increased the incidence of lung cancer in cigarette smokers (RR=1.16, 95% CI 1.02-1.33, p=0.02, Albanes et al. 1996). Out of the 224 patients in the AE database, who developed lung cancer during the trial, 118 were on vitamins compared to 106 on placebo, and of these, 68 were current smokers with 37 on vitamins and 31 on placebo. Suggesting a similar small trend in the same direction.

**7. SAFETY IN PATIENTS WITH LDL-CHOLESTEROL ≤100MG/DL**

Whereas there was a trend for lower mean and median LDL-cholesterol levels after simvastatin treatment during the run-in period in patients who later went on to develop rhabdomyolysis or CK elevations >5xULN in the trial (see Table 33), over 1300 patients with LDL-cholesterol levels below 50mg/dL after the run-in period did not develop rhabdomyolysis or large CK elevations on simvastatin during the trial. Therefore, it is not clear if patients with lower LDL-cholesterol levels at baseline or in response to therapy might be at higher risk of serious adverse events. Reports in the literature support the safety of using statins in patients with low LDL-cholesterol levels. Berg et al. in a letter to *Lancet* Feb 1996, suggested that low LDL-cholesterol levels (<70mg/dL) were not associated with a higher incidence of CK elevations in patients during exercise, and Bakker-Arkema et al. (Atherosclerosis. 2000 Mar;149:123-9) using data pooled from 21 clinical trials with atorvastatin found treatment associated adverse events in patients with at least one LDL-cholesterol level ≤80mg/dL were 24%, comparable to the frequency for all atorvastatin treated patients (20%), and for patients on other statins (24%).

When all serious adverse events (AE.xpt) in patients with baseline LDL-cholesterol levels ≤100mg/dL were reviewed, it appeared that there were fewer distinct patient-events measured by PREFTERM on simvastatin (2,496) compared to placebo (2,722). Each patient event with the same PREFTERM (general headings) and REPTERM (specific headings) was counted only once, but patients could have more than one different event (i.e. same PREFTERM but different REPTERM). More events were seen on placebo (14,477) compared to simvastatin (13,404) in patients with baseline LDL-cholesterol levels >100mg/dL as well. These findings largely reflect the decrease in CHD morbidity and mortality in patients on statins irrespective of their baseline LDL-cholesterol levels.

In order to try to better characterize potential drug related adverse events, all serious adverse events excluding those related to cardiovascular disease, stroke, cancer, diabetes, or non-medical are listed in Table 36.

**Table 36**
**Possible Drug Related Adverse Events in HPS with respect to Baseline LDL-C (≤100, >100mg/dL)**

| PREFTERM | LDL-C ≤100 mg/dL | | LDL-C >100 mg/dL | |
|---|---|---|---|---|
| | Placebo | Simva | Placebo | Simva |
| | N =1701 | N=1720 | N=8566 | N=8549 |
| | N (%) | N (%) | N (%) | N (%) |
| HEPATIC DISEASE | 8 (0.47) | 17 (1.0) | 41 (0.48) | 29 (0.33) |
| LIVER DISEASE | 1 (0.06) | 0 | 0 | 1 (0.01) |
| HOSPITALISATION FOR GALL BLADDER DISEASE | 36 (2.1) | 38 (2.2) | 164 (1.9) | 173 (2.0) |
| | | | | |
| HOSPITALISATION FOR MUSCLE SYMPTOMS (WITHOUT RAISED CK) | 2 (0.12) | 4 (0.23) | 14 (0.16) | 13 (0.15) |
| MYOPATHY (MUSCLE SYMPTOMS WITH RAISED CK) | 1 (0.06) | 3 (0.17) | 3 (0.04) | 6 (0.07) |
| MYOPATHY OR MYALGIA | 0 | 2 (0.12) | 3 (0.35) | 4 (0.47) |
| | | | | |
| RENAL DISEASE | 18 (1.1) | 34 (2.0) | 142 (1.7) | 154 (1.8) |
| RENAL FAILURE | 1 (0.06) | 0 | 0 | 0 |
| | | | | |
| RESPIRATORY DISEASE | 162 (9.5) | 164 (9.5) | 752 (8.8) | 768 (9.0) |
| | | | | |
| SUICIDE | 2 (0.12) | 3 (0.17) | 9 (0.11) | 12 (0.14) |
| | | | | |
| FRACTURE OF HIP, WRIST OR SPINE (NOT ROAD TRAFFIC ACCIDENT) | 21 (1.2) | 19 (1.1) | 71 (0.83) | 92 (1.1) |
| FRACTURE OTHER THAN HIP, WRIST OR SPINE (NOT ROAD TRAFFIC ACCIDENT) | 23 (1.4) | 24 (1.4) | 126 (1.5) | 123 (1.4) |
| | | | | |
| OTHER MEDICAL | 1233 (72) | 1156 (67) | 5979 (70) | 5894 (69) |
| | | | | |
| Total | 1508 | 1464 | 7304 | 7269 |

Data derived from AE.xpt and LABLDL.xpt. Adverse events related to cardiovascular disease, stroke, diabetes, cancer or non-medical were not included. Also 2 adverse events for peripheral nerve Sx (placebo) and 1 adverse events for neurologic disease (simva) and 1 adverse events for peptic ulcer dz (simva) were not included for the sake of brevity.

Again there is no total increase in adverse events in patients in the simvastatin group compared to placebo irrespective of baseline LDL-cholesterol (≤ or > 100mg/dL). There may be a small signal for a slight increase in hospitalizations for muscle symptoms, myopathy or liver disease in

patients with LDL-cholesterol ≤100mg/dL in the simvastatin group compared to placebo but the numbers are quite low. Also there may be a slight increase in renal disease in patients in the simvastatin group compared to placebo for both LDL-C ≤ and > 100mg/dL, but these numbers are also quite low. Looking at the individual REPTERMS that make up the largest group, OTHER MEDICAL also did not identify any clear adverse events that were more common in patients with lower baseline LDL-cholesterol levels in the simvastatin group. Whereas it is still possible that patients with much lower baseline levels of LDL-cholesterol might be at a higher risk, this was also not the case for patients with baseline LDL-cholesterol <50mg/dL in this study. Although the number of these patients is low (N=54), they did not show any clear increase in the number of serious adverse events in patients in the simvastatin group (30 events, including one case of myopathy) compared to placebo (27 events).

In conclusion, whereas there may be a slight increase in the risk of myopathy in patients with low LDL-cholesterol levels on simvastatin this is clearly outweighed by the much larger decrease in cardiovascular-related adverse events.

### D. Safety Update

The final study follow up visits were performed between May and October 2001 and data from these visits was included in the current submission. Since the study was completed in 2001 no further safety updates are required.

## VIII. Dosing, Regimen, and Administration Issues

N/A

## IX. Use in Special Populations

### A. Evaluation of Applicant's Gender Effects Analyses and Adequacy of Investigation

Prior outcome based trials had enrolled low numbers of women (LIPID n=1,516, CARE n=576). which limited the information that could be derived from the safety and efficacy analyses. In HPS, 25% of the total subject population was female (simvastatin group 2542 vs. placebo 2540). Reductions in events for endpoints of CHD mortality, MCE, MVE, nonfatal MIs, were shown to be statistically significant for both men and women on simvastatin compared to placebo. Reductions in events for the endpoints of Total mortality, Stroke, and Revascularization procedures were statistically significant only for men on simvastatin compared to placebo.

The serious adverse events reported in men and women were comparable (see Appendix 4). In general most adverse events in both men and women were less frequent in the simvastatin group supporting the safety of chronic use of the 40mg dose. There were slightly more cases of lung cancer, development of diabetes, myopathy, non-melanoma skin cancer, and renal disease in

both men and women on simvastatin compared to placebo, but the number of cases is too low to be statistically significant. Men also were slightly more likely to have GI adverse events on simvastatin including cancer of the stomach/esophagus and pancreas, hepatic disease and gall bladder disease. In contrast to earlier statin trials the incidence of breast cancer in women was lower in the simvastatin group compared to placebo. Women were also slightly more likely to fracture their hip, wrist or spine in the simvastatin group compared to placebo whereas men were slightly more likely to have fractures other than the hip, wrist or spine in the simvastatin group compared to placebo. Again the number of cases is too low to be statistically significant but this is somewhat surprising as statins had been suggested as a possible treatment to prevent osteoporosis.

### B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The mean and median age for patients was 64 years of age (range 39 to 81) and about 6% were 75 years or older. Patients 65 years of age and older showed significant reductions in risk for all endpoints. Patients under 65 years of age failed to show benefit from simvastatin treatment for Total and CHD mortality endpoints where their event rates were low, but benefit was observed on all non-fatal endpoints except stroke.

An inadequate number of Africans, Orientals and Hispanics were enrolled in this trial to make any efficacy or safety claims for these populations.

**Table 37**
**Study Population by Race**

| Race | Number of patients | % of total population |
|---|---|---|
| **African** | 20 | 0.10 |
| **Chinese** | 10 | 0.05 |
| **West Indian/Guyanese** | 198 | 1.0 |
| **Indian, Pakistani or Bangladeshi** | 332 | 1.6 |
| **Japanese** | 1 | 0.005 |
| **Mixed** | 20 | 0.10 |
| **Other** | 45 | 0.20 |
| **Arab** | 9 | 0.04 |
| **Caucasian** | 19901 | 96.9 |

### C. Evaluation of Pediatric Program

**Pediatric Waiver Request**

The Heart Protection Study was a 5 year clinical outcome study which enrolled adult patients with CHD, or at high risk of a major coronary event because of history of stroke or other cerebrovascular disease, peripheral vascular disease, or diabetes to determine if Zocor 40 mg reduces the risk of mortality and morbidity in this patient population. In order to get sufficient events the study included mostly elderly patients with a mean age of 64 years (SD=8.4 years). It would be highly impractical to conduct such a placebo-controlled study in children, since familial hypercholesterolemia and/or diabetic patients don't get the type of clinical endpoint

events observed in this study until after they've reached adulthood. Therefore, the applicant requested a full waiver from the requirement to perform pediatric studies for the proposed HPS indication, pursuant to 21 CFR 314.55(c). The FDA agrees with the applicant's request and grants a full waiver for this supplemental application.

### D. Comments on Data Available or Needed in Other Populations

There were not enough Africans, Orientals or Hispanics in this trial to generalize the information to these populations (See Table 37).

## X. Conclusions and Recommendations

### A. Conclusions

The clinical information provided from HPS supports the safety and efficacy of Zocor 40mg/day for the treatment of patients at high risk of coronary events because of existing CHD, diabetes, peripheral vascular disease, history of stroke or other cerebrovascular disease to reduce the risk of total mortality by reducing CHD deaths, to reduce the risk of NFMI and stroke, and to reduce the need for coronary and non-coronary revascularization procedures. Whereas the benefits of Zocor 40mg/day were evident in patients in all subgroups with respect to baseline LDL-C, it is still important for patients on chronic therapy with Zocor to have periodic lipid determinations to assess the need for dose adjustment and /or other lipid lowering therapies.

### B. Recommendations

Approvable with revised labeling agreed to by applicant.

# 9 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Statistical-* 19-766
5058

## XI. Appendices

### Appendix 1. Description of minimization procedure

Following is from a document provided by Merck 1/31/03 via email in response to inquiries from FDA

"The minimization algorithm used for random allocation of study treatment in HPS balanced the allocation with respect to the following factors assessed at the screening visit:

- age in 7 categories (aged 40-45; 46-50; 51-55; 56-60; 61-65; 66-70; ≥71);
- sex (male, female);
- total cholesterol in 6 categories (3.5-4.0; 4.01-5.2; 5.21-6.0; 6.01-7.0; 7.01-7.8; ≥7.81 mmol/l);
- diastolic blood pressure in 3 categories (DBP<90 mmHg; ≥90 mmHg; unknown);
- presence or absence of other CHD and MI in 5 categories (other CHD and MI; other CHD without MI; no other CHD with MI; no other CHD without MI);
- presence or absence of cerebrovascular disease in 4 categories (history of stroke or TIA with MI; history of stroke or TIA without MI; no history of stroke or TIA with MI; no history of stroke or TIA without MI);
- presence or absence of peripheral vascular disease (PVD) in 4 categories (history of PVD with MI; history of PVD without MI; no history of PVD with MI; no history of PVD without MI);
- presence or absence of diabetes in 4 categories (history of diabetes with MI; history of diabetes without MI; no history of diabetes with MI; no history of diabetes without MI);
- smoking history in 3 categories (current; ex-smoker; never); and
- ethnic origin in 5 categories (White; Indian; West Indian/Guyanian; Chinese/Japanese; Other).

The algorithm aims to minimize any differences between the treatment groups in these "minimization" characteristics by allocating the patient to that group which would minimize such differences. For example, consider the allocation of a man with diastolic blood pressure >90 mmHg, using a minimization algorithm that balances only with respect to age (male; female) and DBP (≤90 mmHg; >90 mmHg), when a few thousand patients have already been randomized (see table on following page). The allocations that would minimize the differences between the treatment groups in the numbers of men with DBP >90 mmHg are treatments 1 and 2 (which have identical scores for male +DBP>90 mmHg that are lower than those for the other groups), and random allocation between these two treatment groups is then in a ratio of 1:1. (Similarly, if more than two groups had equal scores then random allocation between them would be in equal ratios.) As patients were being entered into HPS from a large number of clinics by staff who were unaware of the previous treatment allocations, of the characteristics of patients who had already been randomized, and of the minimization algorithm being used, this process of

minimization provides optimal balance while allocating study treatment randomly to the HPS population.[1]

| Numbers randomized to date | Treatment 1 | Treatment 2 | Treatment 3 | Treatment 4 |
|---|---|---|---|---|
| Male | 499 | 500 | 504 | 503 |
| Female | 111 | 110 | 115 | 112 |
| | | | | |
| DBP >90 | 361 | 360 | 359 | 364 |
| DBP ≤90 | 249 | 250 | 260 | 251 |
| | | | | |
| Sum for Males, DBP>90 | 860 (499+361) | 860 (500+360) | 863 (504 + 359) | 867 (503 + 364) |

[1] White SJ, Freedman LS. Allocation of patients to treatment groups in a controlled clinical study. *Br J Cancer* 1978; **37**: 849–57"

Following is from a document provided by Merck 3/17/03 via email

"The algorithm aimed to minimize any differences in these "minimization" characteristics between the 4 possible treatment combinations by allocating the patient to the treatment group that would minimize any differences in the assignment "score" (using an algorithm shown to have the best statistical properties[2]). So, *for any particular order of patients*, treatment assignment would be deterministic, except – in the minority of cases (~8%) – when the treatment groups had equal scores. (Analogously, of course, treatment assignment according to a list previously generated from random numbers would also be deterministic for any particular order of patients.) But, this process would still involve random allocation of the study treatment among **all** of the participants since they were entered from a large number of clinics by staff who were unaware of the previous treatment allocations, of the characteristics of those patients who had already been randomized, and of the minimization algorithm being used.[2,3,7] In this respect, what matters when using either a minimization algorithm or an allocation sequence based on random numbers in ensuring proper randomization is that the allocated treatment cannot be predicted prior to entry into the trial (which it could not be in HPS).[8]"

1. Aspirin Myocardial Infarction Study (AMIS) Research Group. AMIS: a randomized controlled trial of aspirin in persons recovered from myocardial infarction. JAMA 1980; 243: 661-9.

2. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975; 31: 103-15 (attached).

3. White SJ, Freedman LS. Allocation of patients to treatment groups in a controlled clinical study. Br J Cancer 1978; 37: 849-57.

4. MRC/BHF Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering therapy and of antioxidant vitamin supplementation in a wide range of patients at increased risk of coronary heart disease death: early safety and efficacy experience. Eur Heart J 1999; 20: 725–41.

5. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. Lancet 2002; 360; 7–22.
6. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes and 14,573 other high-risk individuals: a randomized placebo-controlled trial. Lancet 2003 (submitted).

7. Armitage P. The role of randomization in clinical trials. Stat Med 1982; 1: 345-52.

8. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995; 273: 408-12.

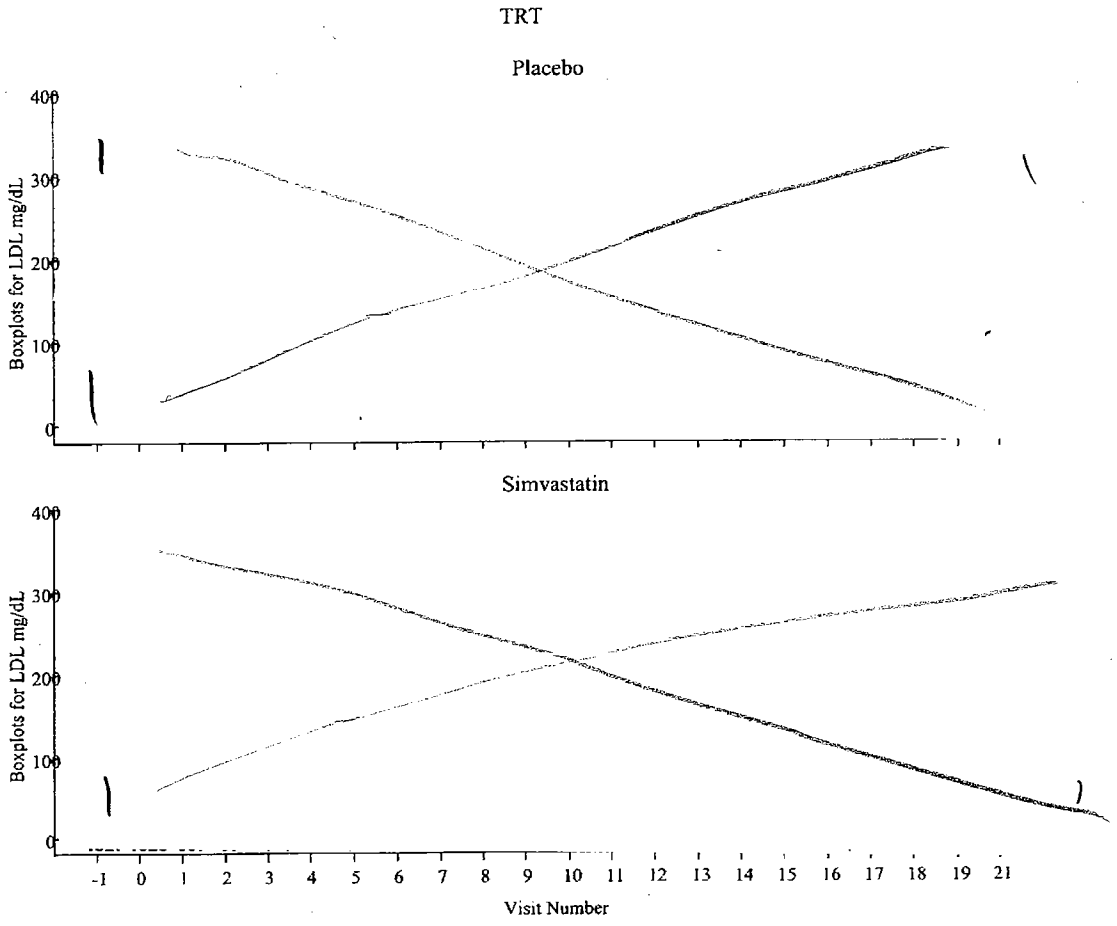
**FDA Statistical Reviewer's Comment:**

**Appendix 2. List of subgroups proposed for analysis by the Data Analysis Plan**

The applicant planned to analyze MCE and MCV for each of the following subgroups listed in the Data Analysis Plan:
(i) in different categories of preexisting disease (i.e., MI, other CHD, no CHD [cerebrovascular, peripheral vascular, diabetes mellitus, treated hypertension: considered together and separately]);
(ii) in various categories determined at screening:
(a) men and women;
(b) age (years): <65, >65 to <70, and =70;
(c) diastolic blood pressure (mm Hg): <80, =80 to <90, =90;
(d) systolic blood pressure (mm Hg): <140, =140 to <160, =160;
(e) total cholesterol (mmol/L): <5.0, =5.0 to <6.0, =6.0;
(f) HDL-C (mmol/L): <0.9, =0.9 to <1.1, =1.1;
(g) LDL-C (mmol/L): <3.0, =3.0 to <3.5, =3.5 (and, as a tertiary comparison, <100; =100 to <130; =130 mg/dL will also be considered);
(h) apolipoprotein A-I (mg/dL): <110, =110 to <130, =130;
(i) apolipoprotein B (mg/dL): <100, =100 to <120, =120;
(j) triglycerides (mmol/L): <2.0, =2.0 to <4.0, =4.0;
(k) creatinine (µmol/L): "normal" (<130 men, <110 women), "elevated" (...130 men, =110 women);
(l) smoking: never regular smoker, ex-cigarette smoker, current smoker;
(m) alcohol (drinks/week): none, 1 to 21, =22;
(n) body mass index (kg/m 2 ): "lean" (<25 male/<24 female), "overweight" (...25 to <30 male / =24 to <28 female), "obese" (...30 male/ =28 female);
(o) waist (cm): "normal" (<94 male/<80 female), "increased" (...94 to <102 male/ =80 to <88 female), "excessive" (...102 male/=88 female);
(p) nondiabetic patients with and without the "metabolic syndrome" (defined as "excessive" waist measurement, plus HDL-C =1.0 mmol/L for men or =1.3 mmol/L for women, plus systolic blood pressure =135 mm Hg or diastolic blood pressure =85 mm Hg);
(q) Hemoglobin A1c (HbA1c) (%) among patients with diabetes: <7.0%, =7.0%;
(r) vitamin E 3 (µmol/L): <24; =24 to <30, =30;
(s) vitamin C 3 (µmol/L): <40, =40 to <60, =60;
(t) beta-carotene 3 (µmol/L): <0.24, =0.24 to <0.40, =0.40;
(iii) in the presence and the absence of the other study treatment; and
(iv) among patients subdivided into 3 similar-sized groups with respect to the size of the reduction in blood cholesterol and the size of the increase in vitamin levels, respectively, during the prerandomization run-in period or active treatment.

**Appendix 3. Boxplots of LDL-C (mg/dL) by visit**

Visit –1 occurred at screening, Visit 0, after the run-in and Visits 1, 2 and 3 occurred at Months 4, 8 and 12. All other visits occurred every 6 months thereafter.



## Appendix 4. Incidence of Serious Adverse Events by Gender and Treatment Group

**Incidence of Serious Adverse Events by Gender and Treatment Group**

| PREFTERM from AE.xpt | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo N=7727 | | Simva N=7727 | | Placebo N=2540 | | Simva N=2542 | |
| | N | (%) | N | (%) | N | (%) | N | (%) |
| AMPUTATION | 106 | 1.37 | 90 | 1.16 | 21 | .83 | 25 | .98 |
| CANCER (NOT NON-MELANOMA SKIN CANCER) | 73 | .94 | 75 | .97 | 16 | .63 | 13 | .51 |
| CANCER OF BLADDER, KIDNEY OR URETHRA | 96 | 1.24 | 88 | 1.14 | 10 | .39 | 8 | .31 |
| CANCER OF BONE OR CONNECTIVE TISSUE | 4 | .05 | 3 | .04 | 1 | .04 | 2 | .08 |
| CANCER OF BREAST | 1 | .01 | | | 50 | 1.97 | 38 | 1.49 |
| CANCER OF CENTRAL NERVOUS SYSTEM | 7 | .09 | 12 | .16 | | | | |
| CANCER OF COLON OR RECTUM | 109 | 1.41 | 93 | 1.20 | 12 | .47 | 10 | .39 |
| CANCER OF LARYNX | 14 | .18 | 14 | .18 | | | 1 | .04 |
| CANCER OF LIP, ORAL CAVITY OR PHARYNX | 8 | .10 | 8 | .10 | | | 3 | .12 |
| CANCER OF LUNG | 92 | 1.19 | 101 | 1.31 | 12 | .47 | 19 | .75 |
| CANCER OF LYMPHATIC OR HAEMATOPOIETIC TISSUE | 39 | .50 | 42 | .54 | 15 | .59 | 12 | .47 |
| CANCER OF OESOPHAGUS OR STOMACH | 37 | .48 | 54 | .70 | 7 | .28 | 7 | .28 |
| CANCER OF OTHER DIGESTIVE ORGANS OR PERITONEUM | 8 | .10 | 7 | .09 | 1 | .04 | 2 | .08 |
| CANCER OF OTHER GENITOURINARY ORGANS | 5 | .06 | 3 | .04 | 1 | .04 | 2 | .08 |
| CANCER OF OTHER RESPIRATORY OR INTRATHORACIC ORGANS | 9 | .12 | 5 | .06 | | | 1 | .04 |
| CANCER OF OTHER SITE | 2 | .03 | 4 | .05 | | | 2 | .08 |
| CANCER OF OVARY | | | | | 6 | .24 | 5 | .20 |
| CANCER OF PANCREAS | 8 | .10 | 15 | .19 | 1 | .04 | 4 | .16 |
| CANCER OF PROSTATE | 143 | 1.85 | 141 | 1.82 | | | | |
| CANCER OF UNSPECIFIED SITE | 23 | .30 | 15 | .19 | 6 | .24 | 5 | .20 |
| CANCER OF UTERUS OR CERVIX | | | | | 12 | .47 | 11 | .43 |
| CAROTID ENDARTERECTOMY/PLASTY | 70 | .91 | 35 | .45 | 12 | .47 | 7 | .28 |
| CORONARY ANGIOPLASTY | 265 | 3.43 | 175 | 2.26 | 57 | 2.24 | 42 | 1.65 |
| CORONARY ARTERY BYPASS GRAFT | 405 | 5.24 | 280 | 3.62 | 47 | 1.85 | 44 | 1.73 |
| CORONARY HEART DISEASE | 1 | .01 | | | 2 | .08 | | |
| DEVELOPMENT OF DIABETES | 158 | 2.04 | 165 | 2.14 | 49 | 1.93 | 55 | 2.16 |
| DIABETES MELLITUS | 73 | .94 | 71 | .92 | 44 | 1.73 | 31 | 1.22 |
| FRACTURE OF HIP, WRIST OR SPINE (NOT ROAD TRAFFIC ACCIDENT) | 48 | .62 | 46 | .60 | 44 | 1.73 | 65 | 2.56 |
| FRACTURE OTHER THAN HIP, WRIST OR SPINE (NOT ROAD TRAFFIC ACCIDENT) | 83 | 1.07 | 90 | 1.16 | 66 | 2.60 | 57 | 2.24 |
| HAEMORRHAGIC STROKE | 22 | .28 | 17 | .22 | 5 | .20 | 4 | .16 |
| HEPATIC DISEASE | 32 | .41 | 40 | .52 | 17 | .67 | 6 | .24 |
| HOSPITALISATION FOR ANGINA | 947 | 12.3 | 786 | 10.2 | 291 | 11.5 | 253 | 9.95 |
| HOSPITALISATION FOR GALL BLADDER DISEASE | 123 | 1.59 | 145 | 1.88 | 77 | 3.03 | 66 | 2.60 |
| HOSPITALISATION FOR MUSCLE SYMPTOMS (WITHOUT RAISED CK) | 13 | .17 | 14 | .18 | 3 | .12 | 3 | .12 |
| ISCHAEMIC STROKE | 320 | 4.14 | 212 | 2.74 | 96 | 3.78 | 85 | 3.34 |
| LEG ULCER | 45 | .58 | 46 | .60 | 20 | .79 | 12 | .47 |

**Incidence of Serious Adverse Events by Gender and Treatment Group**

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| **PREFTERM from AE.xpt** | **Placebo N=7727** | | **Simva N=7727** | | **Placebo N=2540** | | **Simva N=2542** | |
| | **N** | **(%)** | **N** | **(%)** | **N** | **(%)** | **N** | **(%)** |
| LIVER DISEASE | 1 | .01 | 1 | .01 | | | | |
| MELANOMA | 8 | .10 | 13 | .17 | 2 | .08 | 3 | .12 |
| MYOCARDIAL INFARCTION | 517 | 6.69 | 313 | 4.05 | 97 | 3.82 | 68 | 2.68 |
| MYOPATHY (MUSCLE SYMPTOMS WITH RAISED CK) | 3 | .04 | 6 | .08 | 1 | .04 | 3 | .12 |
| MYOPATHY OR MYALGIA | 3 | .04 | 3 | .04 | | | 3 | .12 |
| NEOPLASM | 10 | .13 | 14 | .18 | 7 | .28 | 7 | .28 |
| NON-CORONARY ARTERIAL GRAFT/PLASTY OTHER THAN CAROTID | 395 | 5.11 | 335 | 4.34 | 76 | 2.99 | 66 | 2.60 |
| NON-MEDICAL | 374 | 4.84 | 310 | 4.01 | 135 | 5.31 | 97 | 3.82 |
| NON-MELANOMA CANCER OF SKIN | 185 | 2.39 | 222 | 2.87 | 37 | 1.46 | 51 | 2.01 |
| OTHER MEDICAL | 5228 | 67.7 | 5144 | 66.6 | 1984 | 78.1 | 1906 | 75.0 |
| OTHER NEUROLOGICAL DISEASE OR PROCEDURE | | | 1 | .01 | | | | |
| OTHER VASCULAR DISEASE | 1639 | 21.2 | 1520 | 19.7 | 513 | 20.2 | 444 | 17.5 |
| PEPTIC ULCER, GASTRITIS OR STOMACH PROBLEM | | | 1 | .01 | | | | |
| PERIPHERAL NERVE SURGERY, NEUROPATHY OR SPINAL CORD PROBLEM | 2 | .03 | | | | | | |
| POSSIBLE OR UNCONFIRMED MYOCARDIAL INFARCTION | 37 | .48 | 37 | .48 | 6 | .24 | 5 | .20 |
| RENAL DISEASE | 130 | 1.68 | 152 | 1.97 | 30 | 1.18 | 36 | 1.42 |
| RENAL FAILURE | 1 | .01 | | | | | | |
| RESPIRATORY DISEASE | 673 | 8.71 | 709 | 9.18 | 241 | 9.49 | 223 | 8.77 |
| STROKE OF UNKNOWN ORIGIN | 89 | 1.15 | 84 | 1.09 | 31 | 1.22 | 17 | 0.67 |
| SUBARACHNOID HAEMORRHAGE | 4 | .05 | 5 | .06 | | | 4 | .16 |
| SUICIDE | 8 | .01 | 12 | .16 | 3 | .12 | 3 | .12 |
| TRANSIENT ISCHAEMIC ATTACK | 250 | 3.24 | 226 | 2.92 | 89 | 3.50 | 64 | 2.52 |

Each individual PREFTERM, REPTERM, PTID combination was counted only once, So a patient could be counted more than once if they had more than one REPTERM, but each REPTERM for each patient was counted only once. Data from AE.xpt. Events which appear more frequent in the simvastatin group compared to placebo are highlighted.

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/s/

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William Lubas
4/17/03 05:38:45 PM
MEDICAL OFFICER

Joy Mele
4/17/03 05:40:23 PM
BIOMETRICS

William Lubas
4/17/03 05:43:20 PM
MEDICAL OFFICER

David Orloff
4/17/03 05:53:13 PM
MEDICAL OFFICER
for Dr. Parks

Todd Sahlroot
4/18/03 10:38:18 AM
BIOMETRICS

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 19-766/S-058

# CHEMISTRY REVIEW(S)

## CHEMIST'S REVIEW

**1. ORGANIZATION** CDER/HFD-510
Division of Metabolism and Endocrine Drug Products

**2. NDA #** 19-766
Original NDA approved: 23-DEC-1991

**3. NAME AND ADDRESS OF APPLICANT**
Merck & Co., Inc.
P.O. Box 4
West Point PA 19486 (Phone): 215-652-5000

**4. SUPPLEMENT** SE1-058
18-JUN-2002 (Rec. 18-JUN-2002)

**5. Name of the Drug**
ZOCOR™

**6. Nonproprietary Name**
Simvastatin

**7. SUPPLEMENT PROVIDES** for a revision in the Coronary Heart Disease indication in the Zocor label to include new claims to reduce the risk of mortality and cardiovascular morbidity.

**8. AMENDMENT**

**9. PHARMACOLOGICAL CATEGORY**
HMG-CoA inhibitor used to treat hyperlipidemia

**10. HOW DISPENSED**
Oral

**11. RELATED**
-N. A. -

**12. DOSAGE FORM** Tablet

**13. POTENCY** 5, 10, 20, 40 mg

**14. CHEMICAL NAME AND STRUCTURE**

Butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8α-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1α,3α,7β,8β(2S*,4S*),-8αβ]]; $C_{25}H_{38}O_5$, F.W. = 418.57, CAS 56180-94-0 (For the structure, see Chemistry Review #1, dated 16-MAR-1988 in Vol. 3.1 of NDA 19-766).

**15. COMMENTS** See Chemists Notes. The How Supplied section of the label is revised to include statements approved in S-054, March 21, 2002. An Environmental Assessment wavier is requested.

**16. CONCLUSIONS AND RECOMMENDATIONS** From the Chemistry point of view, this supplement can be approved.

**17. REVIEWER NAME (AND SIGNATURE)** **DATE**
**COMPLETED** 17-SEPT-2002
Sharon Kelly, PhD
**R/D INITIATED BY**

**filename:** 19766#58 NDASup

DISTRIBUTION: Original: sNDA 19-766 cc: HFD-510 Division File CSO Reviewer

**AP**

**Chemist's Notes**

This Prior Approval Supplement, SE1 058, proposes a revision in the Coronary Heart Disease indication in the Zocor label to include new claims to reduce the risk of mortality and cardiovascular morbidity.

The proposed label is updated to include changes to the How Supplied section, as approved in S-054 on Mrch 21, 2002.

Included are 40 mg packages of 100 and 80 mg packages of 100.

The Sponsor requests a categorical exclusion from the requirements to prepare an Environmental Assessment.

**SATISFACTORY.**

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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Sharon Kelly
9/25/02 12:27:56 PM
CHEMIST

Stephen Moore
9/25/02 12:47:21 PM
CHEMIST

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# NDA 19-766/S-058

# ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

NDA: 19-766
ZOCOR® (Simvastatin)
ITEM 13: Patent Information

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PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

| | | |
|---|---|---|
| 1) | Active Ingredient(s) | Simvastatin |
| 2) | Strength(s) | 40mg and 80mg |
| 3) | Trade Name | ZOCOR® |
| 4) | Dosage Form, Route of Administration | Tablets, Oral |
| 5) | Applicant Firm Name | Merck Research Laboratories |
| 6) | NDA Number | 19-766 |
| 7) | Approval Date | |
| 8) | Exclusivity | Three (3) years from the approval of this sNDA |
| | Pediatric Exclusivity Period Expiration • | 6 months following patent expiration; 6/23/2006 |
| 9) | Applicable Patent Number | 4,444,784, expiring 12/23/2005 with PTR<br>Re. 36, 481, expiring 7/10/2007<br>Re. 36, 520, expiring 5/26/2009 |

# PATENT SUBMISSION FORM

Time Sensitive Patent Information pursuant to 21 C.F.R. §314.53 and/or
Patent Information pursuant to 21 C.F.R. §314.53 and §314.60
for

**NDA #** 19-766

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: ZOCOR
- Active Ingredient(s): Simvastatin
- Strength(s): 40mg and 80mg
- Dosage Form(s): Tablet, Oral
- Date __ NDA ✓ sNDA filed: 6/18/2002
- Date __ NDA __ sNDA approved:

**A. This section should be completed for each individual patent**

**U.S. Patent Number:** 4, 444, 784

**Expiration Date:** 12/23/2005

**Type of Patent - indicate all that apply:**

1. Drug Substance (Active Ingredient) ✓ Y__ N
2. Drug Product (Composition/Formulation) ✓ Y__ N
3. Method of Use ✓ Y__ N

**Name of Patent Owner:** /Exclusive License: MERCK & CO., INC., Rahway, NJ

**U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):**

**B. The following declaration statement is required if the above listed patent has Composition/ Formulation or Method of Use claims.**

The undersigned declares that United States Patent Number 4, 444, 784
covers the composition, formulation and/or method of use of _____
(name of drug product). This product is:

- ✓ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act

OR

- __ the subject of this application for which approval is being sought.

**A. This section should be completed for each individual patent**

**U.S. Patent Number:** Re. 36, 481

**Expiration Date:** 07/10/2007

**Type of Patent - indicate all that apply:**

1. Drug Substance (Active Ingredient) ✓ Y __ N
2. Drug Product (Composition/Formulation) __ Y ✓ N
3. Method of Use ✓ Y __ N

**Name of Patent Owner:** MERCK & CO., INC., Rahway, NJ

**U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):**

**B. The following declaration statement is required if the above listed patent has Composition/ Formulation or Method of Use claims.**

The undersigned declares that United States Patent Number Re. 36, 481

covers the composition, formulation and/or method of use of ZOCOR®

(name of drug product). This product is:

- ✓ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act

  OR

- __ the subject of this application for which approval is being sought.

**A. This section should be completed for each individual patent**

**U.S. Patent Number:** Re. 36,520

**Expiration Date:** 05/26/2009

**Type of Patent - indicate all that apply:**

1. Drug Substance (Active Ingredient) ✓ Y__ N
2. Drug Product (Composition/Formulation) __ Y✓ N
3. Method of Use ✓ Y__ N

**Name of Patent Owner:** MERCK & CO., INC., Rahway, NJ

**U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):**

**B. The following declaration statement is required if the above listed patent has Composition/ Formulation or Method of Use claims.**

The undersigned declares that United States Patent Number Re. 36,520

covers the composition, formulation and/or method of use of ZOCOR®

(name of drug product). This product is:

- ✓ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act

  OR

- __ the subject of this application for which approval is being sought.

Respectfully submitted,

By Carol S Quagliato

Carol S. Quagliato
Attorney for Applicants

Merck & Co., Inc.
P.O. Box 2000 - RY60-30
Rahway, NJ 07065-0907
(732) 594- 3809

Date: June 18, 2002

A copy of the above information should be submitted to the FDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

In accordance with 21 C.F.R. §314.53(d)(4), the applicant shall submit two copies of each submission of patent information to:

Central Document Room
Center For Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Room 2-14
12420 Parklawn Dr.
Rockville, MD 20857

**EXCLUSIVITY SUMMARY for NDA # NDA 19-766 SUPPL # S-058**
**Trade Name Zocor Generic Name Simvastatin**
**Applicant Name Merck HFD-510**

**Approval Date April 16, 2003**

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_x_/

   b) Is it an effectiveness supplement? YES /_x_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE-1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_x_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   d) Did the applicant request exclusivity?

YES /_x_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

___3 years___

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /_x __/ NO /_ _/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_x_/

If yes, NDA # _____ Drug Name

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /x/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_x_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-766 Zocor

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES /_x_/ NO /___/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_x/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__x/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_x_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_x_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # Protocol 102

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

| | | |
|---|---|---|
| Investigation #1 | YES /___/ | NO /_x_/ |
| Investigation #2 | YES /___/ | NO /_ _/ |
| Investigation #3 | YES /___/ | NO /___/ |

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_x_/

Investigation #2 YES /___/ NO /_ _/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # Protocol 102

Investigation #_2_, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

| | |
|---|---|
| Investigation #1 | |
| IND # 25,742 YES /_x_/ | NO /___/ Explain: |
| Investigation #2 | |
| IND #___ YES /_ _/ | NO /___/ Explain: |

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

| | |
|---|---|
| Investigation #1 | |
| YES /___/ Explain _____ | NO /___/ Explain _____ |
| _____ | _____ |
| _____ | _____ |
| Investigation #2 | |
| YES /___/ Explain _____ | NO /___/ Explain _____ |
| _____ | _____ |
| _____ | _____ |

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_x_/

If yes, explain: _____

_____

_____

Margaret Simoneau — April 9, 2003
Signature of Preparer — Date
Title: Reg Project Manager

Mary Parks, MD — April 22, 2003
Deputy Director, Medical Team Leader

Signature of Office or Division Director — Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

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David Orloff
4/22/03 05:37:33 PM

Simvastatin – Heart Protection Study
Pediatric Waiver Request

**Pediatric Waiver Request**

The Heart Protection Study is a long-term mortality and morbidity endpoint study in a diverse population of adult patients with, or at high risk of coronary heart disease. The study results demonstrated that, in these patients, therapy with Zocor 40 mg reduces the risk of mortality and morbidity, thus supporting the proposed expanded use of Zocor in this population. With respect to pediatric use for the proposed claim, only pediatric patients with heterozygous or homozygous familial hypercholesterolemia (FH) or diabetes could be considered potential candidates. To support pediatric use under the proposed claim, an analogous randomized, double-blind, placebo-controlled, endpoint study in children would be needed. It would be impossible or highly impractical to conduct this kind of study in children, since heterozygous FH and/or diabetic patients don't get the endpoint events until after they've reached adulthood. For children with homozygous FH, it would be unethical to conduct a placebo-controlled study, and furthermore, the disease prevalence is much too rare (1 in a million) to be practical to conduct an outcomes study.

Please refer to the December 17, 2002 Heart Protection Study Pre-sNDA meeting. In the Pre-sNDA background package, a request for a full waiver from the requirement to perform pediatric studies for the proposed HPS indication, pursuant to 21 CFR 314.55(c), was provided. At the Pre-sNDA meeting, the FDA agreed to grant a full waiver once the HPS supplemental application was filed.

ZOCOR™ (Simvastatin)
Item 16 - Debarment Certification

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc. did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

M. C. Elia

Michael C. Elia, Ph.D., DABT
Senior Director
Regulatory Affairs

6/18/2002
Date

**Simoneau, Margaret A**

**From:** Lubas, William
**Sent:** Thursday, August 01, 2002 4:36 PM
**To:** Simoneau, Margaret A
**Subject:** RE: Financial disclosure continued

Hi,
They don't have any financial arrangements to report but 75 out of 276 (27%) of the investigators did not send in their information. Mostly 70/75 because they were no longer at the clinical site.

I don't know if this will be an issue.

Bill

# Item 19 Financial Disclosure Information

## A. Introduction

In compliance with the U.S. Food and Drug Administration's regulation, *Financial Disclosure by Clinical Investigators*, published 02-Feb-1998 and revised 31-Dec-1998, the following sections detail the requested information concerning the financial interests of and compensation to investigators participating in the covered clinical studies presented in this application.

Investigators meeting the definition of Clinical Investigator (Part 54.2(d)) were requested to complete and return questionnaires related to their financial interest in Merck & Co., Inc. and proprietary interest in the test product. In compliance with the regulatory requirement for the Sponsor to demonstrate "due diligence" (21 CFR Part 54.4), multiple requests for this information were made, when possible, to Clinical Investigators who did not respond. Please note that Merck & Co., Inc. has not entered into any financial arrangement with our clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study (21 CFR 54.2(a)). Merck & Co., Inc. Corporate Finance conducted an internal search for all payments that met the definition of "significant payments of other sorts" (21 CFR 54.2(f)) and reported the information, as appropriate. "Significant payments of other sorts" are calculated cumulatively when an investigator is involved in more than one protocol in the submission.

Data from the clinical study outlined in Table A-1 are presented in this application. The following trial is considered a covered clinical study for the purpose of financial disclosure:

*A Randomised Trial of the Effects on Mortality and Morbidity of HMG CoA Reductase Inhibitors and of Antioxidant Vitamins in a Wide Range of People at High Risk of Coronary Heart Disease (Protocol 102)*

For this clinical protocol, the First Patient In (FPI) was [redacted] and the Last Patient Out (LPO) was [redacted]. In compliance with the Financial Disclosure requirements, "significant payments of other sorts" information has been reviewed for the time period of 02-Feb-1999 through 31-Aug-2001 and included, as appropriate. The cut-off date for financial information provided by the investigators was 05-Mar-2002.

| Table A-1 Summary of Covered Clinical Trial as Defined by 21 CFR 54.2(e) | | | | |
|---|---|---|---|---|
| **Protocol Number** | **Protocol Title** | **FPI** | **LPO** | **"Payments of Other Sorts" Range** |
| 102 | A Randomised Trial of the Effects on Mortality and Morbidity of HMG CoA Reductase Inhibitors and of Antioxidant Vitamins in a Wide Range of People at High Risk of Coronary Heart Disease (Protocol 102) | [redacted] | | 02-Feb-1999 Through 31-Aug-2001 |

Table A-2 - The following trial is considered a non-covered clinical study for the purpose of financial disclosure:

| Table A-2 Summary of Non-Covered Clinical Trials 21 CFR 54.2(e) | |
|---|---|
| **Protocol Number** | **Protocol Title** |
| | Table A-2 is not applicable. |

# 16 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Administrative-* ~~19-766~~
5058

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

**Form Approved: OMB No. 0910-0396**
**Expiration Date: 3/31/02**

# CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

*TO BE COMPLETED BY APPLICANT*

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

*Please mark the applicable checkbox.*

☑ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

| Clinical Investigators | |
|---|---|
| See Tables C-1 and C-2 | |
| Simvastatin - Heart Protection Study | |
| | |

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

| NAME | TITLE |
|---|---|
| David Arkowitz | Controller, MRL Financial Services |
| FIRM/ORGANIZATION: Merck & Co., Inc. | |
| SIGNATURE | DATE: 3/26/02 |

**Paperwork Reduction Act Statement**

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

# 14 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Administrative-* 19-766
5058

# 3 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Administrative-* 19-766
5058

**Division of Metabolic & Endocrine Drug Products**

**Labeling Review**

**Application Number:** 19-766/S-058

**Name of Drug:** Zocor (simvastatin)Tablets

**Sponsor:** Merck

**Submission Date:** April 9, 2003 (e-mail) and April 10, 2003 submission

**Background and Summary:**

Zocor is indicated:

Coronary Heart Disease

In patients with coronary heart disease and hypercholesterolemia, ZOCOR is indicated to:

- Reduce the risk of total mortality by reducing coronary death;
- Reduce the risk of non-fatal myocardial infarction;
- Reduce the risk for undergoing myocardial revascularization procedures;
- Reduce the risk of stroke or transient ischemic attack.

Hyperlipidemia

- ZOCOR is indicated to reduce elevated total-C, LDL-C, Apo B, and TG, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson types IIa and IIb).
- ZOCOR is indicated for the treatment of patients with hypertriglyceridemia (Fredrickson type IV hyperlipidemia).
- ZOCOR is indicated for the treatment of patients with primary dysbetalipoproteinemia (Fredrickson type III hyperlipidemia).
- ZOCOR is also indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

It is supplied in the tablet dose strengths of 5, 10, 20, 40 and 80 mg.

The last approved labeling supplement, S-056, was approved on October 18, 2002, (Package Identifier # 7825442). Supplement–056 provided for the addition of an indication for the treatment of heterozygous familial hypercholesterolemia in a new population of adolescent boys and girls at least one year postmenarchal, ages 10 to 17 years, with a recommended dosing range of 10 to 40 mg once daily of Zocor (simvastatin) tablets. This supplement responded to our Written Request of August 31, 1999, as amended November 26, 2001.

**Review:**

This supplemental new drug application provides for a new indication, based on the results of the Heart Protection Study (HPS), for the use of simvastatin in patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease to reduce the risk of total mortality by reducing coronary death, to reduce the risk of non-fatal myocardial infarction and stroke, and to reduce the need for coronary and non-coronary revascularization procedures.

This supplement provides for revisions to the **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION,** sections of the Package Insert. The specific changes are as follows:

1. In **CLINICAL PHARMACOLOGY,** *Clinical Studies in Adults, "Reductions in Risk of CHD Mortality and Cardiovascular Events"* replaced the subsection title *"Coronary Heart Disease."* Figures 1 and 2, "Years since randomization," were deleted and all new information on the HPS have been added up to the *Angiographic Studies* subsection.

   - In *Angiographic Studies* subsection, figures 3 and 4, "Mean and Minimum Lumen Diameter," were deleted and the entire subsection was changed to read:

     *Angiographic Studies*

     In the Multicenter Anti-Atheroma Study, the effect of simvastatin on atherosclerosis was assessed by quantitative coronary angiography in hypercholesterolemic patients with coronary heart disease. In this randomized, double-blind, controlled study, patients were treated with simvastatin 20 mg/day or placebo. Angiograms were evaluated at baseline, two and four years. The co-primary study endpoints were mean change per-patient in minimum and mean lumen diameters, indicating focal and diffuse disease, respectively. Simvastatin significantly slowed the progression of lesions as measured in the Year 4 angiogram by both parameters, as well as by change in percent diameter stenosis. In addition, simvastatin significantly decreased the proportion of patients with new lesions and with new total occlusions.

   - After *Angiographic Studies* subsection, *Modifications of Lipid Profiles* subsection was added.

2. **INDICATIONS AND USAGE section** has been changed to read:

Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

In patients with CHD or at high risk of CHD, ZOCOR can be started simultaneously with diet.

*Reductions in Risk of CHD Mortality and Cardiovascular Events*

In patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, ZOCOR is indicated to:

- Reduce the risk of total mortality by reducing CHD deaths.
- Reduce the risk of non-fatal myocardial infarction and stroke.
- Reduce the need for coronary and non-coronary revascularization procedures.

*Patients with Hypercholesterolemia Requiring Modifications of Lipid Profiles*

ZOCOR is indicated to:

- Reduce elevated total-C, LDL-C, Apo B, and TG, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson types IIa and IIb[***4]).
- Treat patients with hypertriglyceridemia (Fredrickson type IV hyperlipidemia).
- Treat patients with primary dysbetalipoproteinemia (Fredrickson type III hyperlipidemia).
- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

♦ Under *General Recommendations* subsection, "poorly controlled diabetes mellitus" was deleted from the first sentence.

3. In **WARNINGS**, *Liver Dysfunction* subsection, the fourth paragraph, first two sentences were changed to read:

**It is recommended that liver function tests be performed before the initiation of treatment, and thereafter when clinically indicated. Patients titrated to the 80-mg dose should receive an additional test prior to titration, 3 months after titration to the 80-mg dose, and periodically thereafter (e.g., semiannually) for the first year of treatment.**

4. In **PRECAUTIONS**, *Geriatric Use* subsection, after the first sentence, the paragraph has been changed to read:

In 4S, 1,021 (23%) of 4,444 patients were 65 or older. In 4S, lipid-lowering efficacy was at least as great in elderly patients compared with younger patients. In this study, ZOCOR significantly reduced total mortality and CHD mortality in elderly patients with a history of CHD. There were no overall differences in safety between older and

younger patients in 4S. In HPS, 52% of patients were elderly (4,891 patients 65-69 years and 5,806 patients 70 years or older). The relative risk reductions of CHD death, non-fatal MI, coronary and non-coronary revascularization procedures, and stroke were similar in older and younger patients (see CLINICAL PHARMACOLOGY). In HPS, among 32,145 patients entering the active run-in period, there were 2 cases of myopathy/rhabdomyolysis; these patients were aged 67 and 73. Of the 7 cases of myopathy/rhabdomyolysis among 10,269 patients allocated to simvastatin, 4 were aged 65 or more (at baseline), of whom one was over 75.

5. In **ADVERSE REACTIONS**, a new *Heart Protection Study, Clinical Adverse Experiences* subsection has been added to read:

*Heart Protection Study*
*Clinical Adverse Experiences*

In HPS (see CLINICAL PHARMACOLOGY, *Clinical Studies*), involving 20,536 patients treated with ZOCOR 40 mg/day (n=10,269) or placebo (n=10,267), the safety profiles were comparable between patients treated with ZOCOR and patients treated with placebo over the mean 5 years of the study. In this large trial, only serious adverse events and discontinuations due to any adverse events were recorded. Discontinuation rates due to adverse experiences were comparable (4.8% in patients treated with ZOCOR compared with 5.1% in patients treated with placebo). The incidence of myopathy/rhabdomyolysis was <0.1% in patients treated with ZOCOR.

6. In **DOSAGE AND ADMINISTRATION**, the first two paragraphs and *Patients with Homozygous Familial Hypercholesterolemia* subsection, have been changed to read:

The patient should be placed on a standard cholesterol-lowering diet. In patients with CHD or at high risk of CHD, ZOCOR can be started simultaneously with diet. The dosage should be individualized according to the goals of therapy and the patient's response. (For the treatment of adult dyslipidemia, see NCEP Treatment Guidelines. For the reduction in risks of major coronary events, see CLINICAL PHARMACOLOGY, *Clinical Studies in Adults.*) The dosage range is 5-80 mg/day (see below).

The recommended usual starting dose is 20 to 40 mg once a day in the evening. For patients at high risk for a CHD event due to existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, the recommended starting dose is 40 mg/day. Lipid determinations should be performed after 4 weeks of therapy and periodically thereafter. See below for dosage recommendations in special populations (i.e., homozygous familial hypercholesterolemia, adolescents and renal insufficiency) or for patients receiving concomitant therapy (i.e., cyclosporine, amiodarone, verapamil, fibrates or niacin).

*Patients with Homozygous Familial Hypercholesterolemia*

The recommended dosage for patients with homozygous familial hypercholesterolemia is ZOCOR 40 mg/day in the evening or 80 mg/day in 3 divided doses of 20 mg, 20 mg, and an evening dose of 40 mg. ZOCOR should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

- *Concomitant Lipid-Lowering Therapy* subsection was relocated in the label to follow the *Adolescents (10 –17 years of age) with Heterozygous Familial Hypercholesterolemia* subsection. There were no text changes.

**Conclusion**:

The proposed draft label (Package Identifier #782544X; Merck ID Number 9556643), submitted April 10, 2003, was found acceptable by the reviewing team. The labeling review is from the electronic *MS* Word version of the electronic draft labeling for S-056, package insert submitted October 17, 2002, approved on October 18, 2002. The Agency will issue an approval action on this supplement.

Reviewed by: M.A. Simoneau, R.Ph., Regulatory Project Manager/EG 4.13.03
(See appended electronic signature page)

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/s/

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Margaret Simoneau
4/16/03 04:48:51 PM
CSO

**MEMO TO DIVISION FILES**

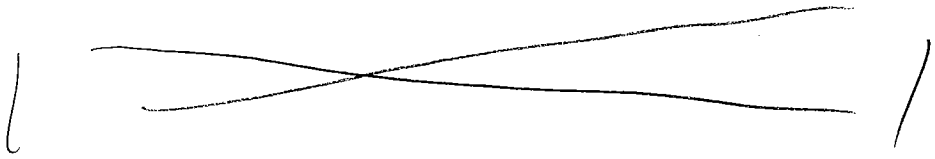
**NDA# 19,766**
**Serial No. 058**
**Sponsor**: Merck & Co., Inc
**Drug Name**: Zocor (simvastatin)
**Category**: lipid-lowering agents August 23, 2002

**Request for Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics and Devices:**

**Introduction**:
The sponsor has submitted a package containing material to be disseminated to health care practitioners, pharmacy benefit managers, health insurance issuers, group health plans, and Federal or State Government agencies in accordance with 21 CFR Part 99.105.

The package is to contain a reprint of the article "MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo controlled trial" published in the July 6, 2002 issue of *The Lancet*, and "mandatory statements and information", including the official labeling and a bibliography of other articles both supporting and not supporting the new use in accordance with 21 CFR Part 99.103.

On June 18, 2002 the sponsor submitted a supplemental application, N19766 S-058, with clinical data supporting the new use for review by the agency, in accordance with 21 CFR 99.201.



**Medical Reviewer's Comments**
The new use proposed by the sponsor is a viable candidate for a labeling supplement and such a supplement has already been submitted to the agency.

The new use defined by the sponsor is consistent with the data presented in the reprint (see Figures 2, 3, 7 and 8 in the reprint).

The reprint and accompanying bibliography contain balancing statements. Reference is made in the reprint to the CARE study in which no decrease in mortality was seen for patients with a previous myocardial infarction who had plasma LDL levels below 125mg/dl and to the Prospective Pravastatin Pooling Project which used data from both

CARE and LIPID studies to suggest there was no relative risk reduction in patients with baseline LDL below 125mg/dl.

**Conclusions:**
After review of this package there is no reason to object to the dissemination of the information.

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/s/
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William Lubas
8/23/02 10:11:07 AM
MEDICAL OFFICER

The deadline for the review was today.

Anne Pariser
8/28/02 07:32:40 AM
MEDICAL OFFICER

**Meeting Minutes**

Division of Metabolic and Endocrine Drug Products
**NDA 19-766**

Date: Thursday, August 1, 2002
Location: Parklawn 14B45
Time: 3 to 4 PM
FDA Attendees:

Drs. David Orloff, Mary Parks and William Lubas, Todd Sahlroot, Joy Mele, Karen David-Bruno, Hae Young Ahn, Sharon Kelly, Enid Galliers and Margaret Simoneau.

This was a **Filing meeting** for Zocor (simvastatin) tablets, efficacy supplement S-058, dated June 18, 2002. This supplement proposes to add additional information to various sections of the Package Insert from the Heart Protection Study (HPS) evaluating the effects on mortality and morbidity of Zocor in a wide range of patients at high risk of coronary heart disease. Additional reference is made to our December 17, 2001, meeting minutes with the sponsor.

- **Clinical**- Dr. Lubas is the primary medical reviewer. There were no filing issues and financial disclosure information was submitted. The sponsor did not have any financial arrangements to report but 75 out of 276 (27%) of the investigators did not send in their information. Mostly 70/75 because they were no longer at the clinical site.
- **Pharmacology**- Not needed.
- **Chemistry**- Sponsor requested a categorical exclusion from the requirements to prepare an Environmental Assessment.
- **Biopharm**- Not needed.
- **Biostatistics**- Unworkable fixed data sets would not allow the primary reviewer to begin the review process for a recommendation.
- **DSI**- No audit would be required.
- **Advisory Committee**- Not needed.
- **Review Goal Date with labeling**-

The file date for this supplement is August 18, 2002. If the sponsor can provide the statistical information within a reasonable timeframe of this date, then the submission will be filed. The supplement will be a standard review. The user fee goal date is April 19, 2003. Primary reviews are due in DFS by March 7, 2003.

Minutes preparer: Margaret Simoneau, R.Ph.
Regulatory Project Manager
(*See appended signature page*)

Concurrence Chairman: Mary Parks, M.D.
Deputy Director/Medical Team Leader
(*See appended signature page*)

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/s/

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Mary Parks
8/12/02 03:32:32 PM

# Meeting Minutes

| | |
|---|---|
| **NDA # 19-766** | Zocor (simvastatin) Tablets |
| **Meeting Date:** | December 17, 2001 |
| **Time:** | 1:00 PM |
| **Location:** | Parklawn, Third Floor, Chesapeake Conference Room |
| **Sponsor:** | Merck & Co., Inc. |
| **Type of Meeting:** | Type C |
| **Meeting Chair:** | David Orloff, M.D., Office Director, DMEDP |
| **Sponsor Contact:** | Michael Elia, Ph.D.,DABT, Director, Regulatory Affairs |
| **Regulatory Project Manager:** | Margaret Simoneau, M.S., R.Ph. @ 301-827-6411 |
| **FDA Participants:** | David Orloff, M.D., Division Director, DMEDP<br>Mary Parks, M.D., Medical Team Leader<br>Todd Sahlroot, Ph.D., Biometrics Team Leader<br>Margaret Simoneau, M.S., R.Ph, Reg. Project Manager |
| **Sponsor Participants:** | Michael Elia, Ph.D, DABT, Regulatory Affairs<br>Susan Nolt, Regulatory Affairs<br>Thomas Hassall, R.Ph., Regulatory Agency Relations<br>Dr. Jane Armitage, University of Oxford<br>Edward Chafart, Data Management<br>Dr. Rory Collins, University of Oxford<br>Cathy Cullum, Data Management<br>Betsy Fallen, Regulatory Coordination<br>Dr. Mary Jane Geiger, Project Management<br>Daniel Orfe, Electronic Regulatory Submissions<br>Dr. Deborah Shapiro, Biostatistics<br>Ann Tate, Clinical Research<br>Dr. Jonathan Tobert, Clinical Research<br>Karl Wallendszuz. University of Oxford |

**Meeting Objective:**

This meeting was requested by the sponsor to discuss a future efficacy supplement submission based on the results of the Heart Protection Study (HPS). This trial is a multicenter study consisting of about 20,000 patients at high risk of coronary heart disease (CHD) randomized to simvastatin or placebo for at least five years. All 20,000 patients are also randomized to antioxidant vitamin supplementation (vitamins E and C and beta-carotene) or placebo as part of a 2 x 2 factorial design. The study is being conducted in the United Kingdom by the Clinical Trials Service Unit (CTSU) at the University of Oxford. The meeting was to discuss the format and content of the planned submission and the appropriate methods for statistical analysis of the data.

**Discussion Points (Questions submitted):**

1. **Priority Review**

   Given (1) that there are no approved products to reduce the risk of mortality and the clinical events described above in patients with or without hypercholesterolemia with CHD, or a history (with or without CHD) of diabetes, stroke or peripheral vascular disease, (2) the serious nature of these diseases, and (3) that approval of Zocor for this indication would be a significant improvement in the treatment of these diseases, does the FDA agree that the planned sNDA meets the requirements for classification as a Priority Review Efficacy Supplement? *Priority or standard review status is determined at the filing of the efficacy supplement.*

2. **One Pivotal Study**

   Does the FDA agree that the Heart Protection Study results provides substantial and adequate evidence to support the proposed indication? *Yes.*

3. **Statistical Analyses**

   a.) Does the FDA concur with the planned statistical approach to the data analyses, presentation and formatting as described in the Summary for Planned Statistical Approach Section (Tab 5) and in the Data Analysis Plan? *Complete documentation of the interim analysis plan should be submitted as part of the application.*

   b.) No analyses or listings of results will be provided by site/center since the more appropriate surrogate is analysis by type of patient and this is fully explored by the multitude of subgroup analyses which are being provided. Also note that a centralized randomization scheme (rather than randomization within study center) was employed in this study. Does the FDA agree with this approach? *This was acceptable by the Agency.*

   c.) Does the FDA request any additional analyses beyond what is presented in the submitted DAP? *The sponsor is requested to perform subgroup analysis on total mortality in addition to subgroup analysis already performed. It is not necessary to submit subgroup analyses of ethnic groups.*

4. **Plans for Electronic Submission of the sNDA**

Does the FDA agree with the proposed plan for the electronic submission of the sNDA as described in the Summary of the Plans for Electronic Submission Section (Tab 6)? *Agency requested separate efficacy data sets for each outcome variable similar to the format of the AFCAPS submission. Submission should include all subgroups with demographic information included. The sponsor is encouraged to contact the statistical reviewer, Ms. Mele, prior to finalizing the electronic dataset. It is not anticipated at this time that the statistical reviewer will require review aids. However, if the need should arise to facilitate the review of this complex dataset, the sponsor will work with the University of Oxford and FDA to construct appropriate review aids.*

5. **Pediatric Waiver Request**

Does the FDA agree with Merck's request for a full waiver from the requirement to perform pediatric studies for the proposed indication as described in the Pediatric Studies – Request for a Waiver Section (Tab 8)? *Yes.*

**Prepared by:** *(See appended electronic signature page)*
**Margaret Simoneau, M.S., R.Ph., Regulatory Project Manager**

**Approval:** *(See appended electronic signature page)*
**David Orloff, M.D., Division Director, HFD-510, Meeting Chair**

Concurrence: M. Parks 1.16.02/T.Sahlroot 1.16.02

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/s/

David Orloff
1/18/02 10:57:31 AM

# 22 Page(s) Withheld

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__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Administrative-* 14-766
5058

T03-xx
April 10, 2003

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

**FDA Announces Labeling Changes on Heart Benefit Associated with Cholesterol Drug Zocor**

The Food and Drug Administration (FDA) has announced changes to the labeling for Zocor (simvastatin), based on the results of The Heart Protection Study (HPS). The new labeling will state that simvastatin is effective in reducing risks of fatal and non-fatal heart attacks, strokes, and in reducing the need for bypass surgery and angioplasty. FDA approved Zocor in 1988 to lower cholesterol.

The Heart Protection Study was a double-blind, placebo-controlled study conducted in 20,536 patients. Men and women with heart disease or at high risk because of diabetes, peripheral arterial disease, or a history of stroke or other cerebrovascular disease were treated with either simvastatin 40 mg/day or placebo for an average of 5 years. The average age of patients entering HPS was 64 years and the average LDL-C (low density lipoprotein C, or

-More-

"bad" cholesterol) level at baseline was 131 mg/dL. The trial population included a large number of diabetics and elderly patients.

The risk of death from coronary heart disease was reduced by 18 percent in the patients treated with simvastatin. The risk of having a non-fatal heart attack was reduced by 38 percent in this group. Simvastatin also reduced the risk of stroke by 25 percent and the need for undergoing coronary or non-coronary revascularization procedures (procedures to unblock clogged arteries) by 30 and 16 percent, respectively.

The effect of simvastatin to reduce the rate of cardiovascular events was seen in a number of relevant subpopulations of patients enrolled in the trial, including those with and without heart disease, diabetics and non-diabetics, and regardless of gender, age, or baseline cholesterol levels. An important observation in this trial was that patients who had diabetes, peripheral vessel disease, and cerebrovascular disease but who had no evidence of heart disease benefited from taking simvastatin.

**-More-**

Simvastatin has been shown to be effective in reducing total cholesterol and LDL cholesterol in familial and non-familial forms of hypercholesterolemia (high cholesterol) and in mixed hyperlipidemia -(elevations in both cholesterol and triglycerides).

As with other statins, Zocor should be used in conjunction with a standard cholesterol-lowering diet. The dose of Zocor should be individualized according to the goals of therapy and the patient's response. The dosage range is 5-80 mg/day.

As with all statin drug products, patients should be aware of any muscle pain, which may indicate an adverse reaction called rhabdomyolysis, a muscle breakdown disorder. Symptoms can include fatigue, fever, nausea and vomiting, severe muscle pain, weakness and tenderness. Rhabdomyolysis can cause electrolyte imbalances that can result in heart rhythm problems, cardiac arrest, or heart attack. Although the beneficial effects of Simvastatin in HPS were observed with the 40 mg dose, lower doses are recommended in special populations such as those taking certain medications including cyclosporine, verapamil,

**-More-**

amiodarone, and other cholesterol-lowering drugs and in patients with kidney problems.

Zocor is manufactured by Merck and Co., Inc. of Whitehouse Station, N.J.

####

Michael C. Elia, Ph.D., DABT
Senior Director
Regulatory Affairs

DESK COPY

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486
Tel 484 344 3180
215 652 5000
Fax 484 344 2516
Email: michael_elia@merck.com

April 10, 2003


David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Orloff:

**NDA 19-766/S-058: ZOCOR™ (Simvastatin)**

**Amendment to a Pending Application**

Reference is made to the supplemental New Drug Application cited above for ZOCOR™ submitted as an electronic archive on June 18, 2002. Reference is also made to the email communication of April 9, 2003 from Dr. Michael C. Elia, Merck Research Laboratories (MRL) to Ms. Margaret Simoneau, Senior Regulatory Project Manager FDA containing final draft labeling for the ZOCOR™ Heart Protection Study (HPS).

As indicated on the attached Form FDA 356h, this amendment provides for changes in the ***Labeling*** Section of the approved New Drug Application for ZOCOR™ .

The proposed text reflects the revisions as agreed upon during FDA teleconferences on March 31, April 1-2, and April 4, 2003. The original sNDA was submitted to FDA on 18-June-2002 in NDA # 19-766/S-058 and amended on 31-January-2003.

The revised, annotated Package Circular shows all HPS-related labeling changes with revision marks. Additional editorial changes are also shown with revision marks and annotated accordingly. It is important to note that this revised draft labeling is based on the last approved circular (#782544X), which corresponds to NDA #19-766/S-056 (pediatric), approved by FDA on 18-Oct-2002. The last approved circular has not yet been printed. In contrast, the original HPS supplement (S-058, dated 18-Jun-2002) utilized the "last approved/approvable text as of April 2002" as the base document on which the HPS revisions were shown.

In summary, this amendment to a pending supplement for HPS includes revisions to the circular based on FDA labeling negotiations to date.

The Statement of Organization following this letter describes the sections contained in this application.

With this submission are the following items:

- Proposed Labeling Text of the Package Circular
- Annotated Package Circular
- Proposed Labeling Text of the Package Circular in Microsoft Word (to be sent as a review aid)
- Annotated Microsoft Word Version of the Proposed Labeling Text. Located in the summary folder. File name "annotated .doc"

Labeling
II. Labeling text
    a. Proposed labeling text

Summary
I. Annotated package circular

The Microsoft WORD version of the proposed labeling text is also supplied as PROPOSED.DOC within the labeling folder on the Compact Disk (CD) provided.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 7.51, Symantec Corp., 2000) and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolic and Endocrine Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Margaret Simoneau, R.Ph., M.S., Senior Regulatory Project Manager, Division of Metabolic and Endocrine Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Michael C. Elia, Ph.D., DABT (484-344-3180) or, in my absence, to Edwin L. Hemwall, Ph.D. (484-344-2306).

Sincerely,

M. C. Elia

Michael C. Elia, Ph.D., DABT
Senior Director, Regulatory Affairs

Enclosure: CD

Federal Express # 1

Q:_BConroy\ZOCOR\NDA Letters\amend\10-Apr-03_HPS_draft_label.doc

Desk Copies: Margaret Simoneau, R.Ph., M.S.
Regulatory Project Manager (cover letter)
HFD-510, Room 14B-19
Federal Express #2

Michael C. Elia, Ph.D., DABT
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486
Tel 484 344 3180
215 652 5000
Fax 484 344 2516
Email: michael_elia@merck.com

April 10, 2003

**DESK COPY**

MERCK
Research Laboratories

David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Orloff:

**NDA 19-766/S-058: ZOCOR™ (Simvastatin)**

**Amendment to a Pending Application**

Reference is made to the supplemental New Drug Application cited above for ZOCOR™ submitted as an electronic archive on June 18, 2002. Reference is also made to the two email responses sent on March 27, 2003 by Dr. Michael C. Elia, Merck Research Laboratories (MRL) to Dr. William Lubas, Medical Reviewer, FDA in reply to the email communication sent on March 21, 2003 by Dr. Lubas regarding the information requested below.

**FDA Question from Dr. Lubas - 1st set: Safety data:**

*Q. The new label proposes to insert the following statement "Discontinuation rates due to adverse experiences were comparable (4.8% in patients treated with ZOCOR compared with 5.1% in patients treated with placebo)." Under ADVERSE EXPERIENCES. Could you tell me how I could verify your numbers with the datasets you sent me? The discontinuation dataset EPDISCON lists the patients who discontinued simva under STOPTAB=1 but it does not list AE as a cause. It instead lists more specific causes like elevated liver enzymes (STENZLIV), muscle pain/weakness (STMUSC), etc. While the AE dataset does not list when the study drug were discontinued. Did you just assume that anyone who discontinued simva and had an AE discontinued because of the AE?*

**Merck Response**

The definition of stopping treatment due to an adverse event is as follows: anyone stopping due to muscle or liver enzyme abnormalities, muscle symptoms or, if not taking a non-study statin, then if any symptom or diagnosis was given as the reason for stopping, that reason was used. In theory this can be reproduced from the EPDISCON file using the following condition:

STENZLIV=1 or STENZMUS=1 or STMUSC=1 or (STSYMP=1 and STSTATIN<>1)

However, the Oxford statistical programmer discovered that there was an error in the program which created the EPDISCON file. Consequently, if you try to recreate the numbers of patients stopping due to an adverse event (using Oxford's definition) it will undercount. The error involves about 90 patients. The correct numbers for the discons are 496 patients on simvastatin vs. 520 patients on placebo. This translates into the discontinuation rates cited in the Lancet paper and in our proposed labeling, i.e., 4.8% with simvastatin vs. 5.1% with placebo). However, if this analysis is run off the current EPDISCON file, Oxford indicates that the discon numbers will be 451 on simvastatin vs. 485 on placebo.

Based on our discussions with Oxford and our previous validation work it appears this is an unfortunate but isolated error.

Provided in Item 11 of this submission are the corrected files needed to reproduce the HPS discontinuation rates cited in the revised ZOCOR™ label.

With this submission are the following items:

- EPDISJUN.XPT - SAS transport file with replacement columns
- DEFINE.PDF - definition of the content of the EPDISJUN.XPT
- EPDISCON_MERGE.SAS - SAS program to merge the new dataset columns into the Sept, 2002 - EPDISCON.XPT
- README.PDF - Document describing the steps to Execute the Epdiscon Merge Program

The remainder of the information requested in the March 21, 2003 email communication will be submitted under separate cover.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 7.51, Symantec Corp., 2000) and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolic and Endocrine Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Margaret Simoneau, R.Ph., M.S., Senior Regulatory Project Manager, Division of Metabolic and Endocrine Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Michael C. Elia, Ph.D., DABT (484-344-3180) or, in my absence, to Edwin L. Hemwall, Ph.D. (484-344-2306).

Sincerely,

M. C. Elia

Michael C. Elia, Ph.D., DABT
Senior Director, Regulatory Affairs

Enclosure: CD

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April 10, 2003

David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products

MERCK
Research Laboratories

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

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**Response to FDA Request For Information**

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Merck is providing the information forwarded via the March 27, 2003 email, which has now been reformatted for archival purposes. In addition, provided in Item 20 is a spreadsheet which lists both the Merck-assigned site numbers and the corresponding Oxford site numbers.

**FDA Questions from Dr. Lubas - 1st set: Safety data and Financial Disclosure info:**

*Q. Thanks for the additional information on the 41 cases of hepatitis.*
*My concern is that only 6 of them had data in the LABALT dataset with ALT >3xULN which means that most LFT data from out of study office visits/hospitalizations were not included in that dataset, which means that this dataset underestimates the true incidence of ALT elevations in this study population. This would explain why the incidence of ALT elevations on simva and placebo in HPS are lower than is already in the label for 4S (0.7% simva vs. 0.6% placebo) and "2 other clinical trials" 0.9% simva.*

**Merck Response**
The absolute incidence of transaminase elevations within a study depends on many factors, including the frequency of monitoring and the nature of the study population, for example with regard to its consumption of alcohol. Nevertheless, the *difference* in confirmed ALT elevations between treatment groups in HPS of approximately 0.1% was very similar to that in 4S. The two other trials referred to in the label are the Phase III studies for the 80 mg dose extension program, for which 40 mg was the control. There was no placebo group in these studies.

By definition, monitoring comprises measurements in asymptomatic patients, which in clinical trials are performed at specified regular intervals. There was never any intention in HPS to capture elevations of ALT that occurred between visits in association with liver disease not considered related to study medication.

In any event, as noted in our previous response and shown in Table 1, hospitalizations for liver disease were distributed essentially equally among patients allocated to simvastatin and placebo. Using the information provided previously about the cases of liver problems during HPS, the table illustrates that there were similar numbers of patients allocated active versus placebo simvastatin in each sub-category. Therefore, there is no reason to believe that inclusion of out-of-study ALT elevations would have materially altered the comparison between simvastatin and placebo.

Table 1. Patients reporting any liver associated problems during HPS.

| Type of liver problem reported or underlying cause based on additional information | simvastatin | placebo |
|---|---|---|
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| Alcohol induced | 4 | 1 |
| Liver biopsy | 1 | 5 |
| Unspecified liver problem | 6 | 4 |
| Biliary problem | 2 | 2 |
| Chronic liver disease/cirrhosis | 1 | 2 |
| Cancer associated | 2 | 2 |
| Any liver problem | 20 | 21* |

*one patient counted under biliary disease and cancer associated

*Q. This same thing happened with CK elevations in the LABCK dataset. Only 3 of the 9 patients on simva and 1 of the 3 pts on placebo with CK>10xULN are reported in this dataset. I had to find the actual values in Table 35 of section 8.2 of your submission.*

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As with ALT, the dataset includes only CK values recorded at the study visits. Most cases of myopathy occurred between visits. Because elevations of CK > 10 x ULN were usually associated with symptoms, leading to a diagnosis of drug-related myopathy, they were captured from the local sites that measured them.

*Q. Could you check for me why three patients (201147, 371195, 541272) were discontinued for "awaiting CK" (EPDISCON dataset, STOTH1=8B3C) when the highest value of CK I could find for any of these patients was 298=1.2xULN. Did they have CK elevations during hospitalizations?*

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**Merck Response**
The site numbers under the financial disclosure form were assigned by Merck and so do not match those in the datasets. The attached spreadsheet (see Item 20) lists both the Merck-assigned site numbers and the corresponding Oxford site numbers. Nearly all collaborators and nurses at the 69 participating sites did complete the financial disclosure forms.

**FDA Questions from Dr. Lubas - 2nd set: Hospitalizations for Angina**

*Could you please describe for me how hospitalizations for angina were determined.*

*1) Did this include only patients who had unstable angina to start with or all pts?*

**Merck Response**
Any patient in HPS who was hospitalized for angina was included in this endpoint. (Patients with unstable angina within the previous six months were not eligible to enter HPS.)

*2) How was angina confirmed? Were there any ECG criteria?*

**Merck Response**

There were no specific ECG criteria. For this tertiary endpoint, the definition was met if the hospital discharge summary indicated that the patient was admitted for angina.

*3) This was a time to first event analysis not total number of events,* right?

**Merck Response**
This is correct.

*4) How did you define "Possible MI"?*

**Merck Response**
Possible MI indicates a hospital discharge summary indicating MI without the criteria for MI (established in the SOP used by the adjudicating CTSU physician) having been met. This was not a predefined endpoint and no claim in the proposed label is based on it.

We hope that responses provided in this submission have adequately addressed the Agency's comments and requests.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

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Senior Director, Regulatory Affairs

Enclosure: CD

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Desk Copies: Margaret Simoneau, R.Ph., M.S.
Regulatory Project Manager (cover letter)
HFD-510, Room 14B-19
Federal Express #2

## Simoneau, Margaret A

**From:** Mele, Joy D
**Sent:** Friday, March 28, 2003 9:39 AM
**To:** Simoneau, Margaret A; Lubas, William (CDER); Parks, Mary H; Sahlroot, Jon T; Orloff, David G
**Subject:** RE: DDMAC Comments on revised draft label

Andy-
The diabetic population were almost all type 2 patients (more than 90%) - maybe we should mention that?? Their HbA1c control did not seem to play a role in the efficacy of ZOCOR though we only know about their HbA1c levels at baseline not while on study. We show in two places that diabetic pts with CHD do not benefit as much as diabetics w/o CHD. Does that seem good enough?

Joy

-----Original Message-----
**From:** Simoneau, Margaret A
**Sent:** Friday, March 28, 2003 9:26 AM
**To:** Lubas, William (CDER); Parks, Mary H; Mele, Joy D; Sahlroot, Jon T
**Subject:** FW: DDMAC Comments on revised draft label

-----Original Message-----
**From:** Haffer, Andrew
**Sent:** Friday, March 28, 2003 9:23 AM
**To:** Simoneau, Margaret A
**Cc:** Lubas, William (CDER)
**Subject:** DDMAC Comments on revised draft label

Peggy,

I have a few comments regarding the revised label. Please forward them to the team.

Thanks,

Andy

++++++++++++++++++++++++++++++++++++++++++++++++++++++++
DDMAC Comments on HPS Proposed Label Changes:

1. Are both types 1 and 2 diabetics, at any level of severity, acceptable criteria for patients at high risk of developing a major coronary event? The term "Diabetes" seems a little broad.

++++++++++++++++++++++++++++++++++++++++++++++++++++++++

## Simoneau, Margaret A

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**Sent:** Friday, March 28, 2003 9:23 AM
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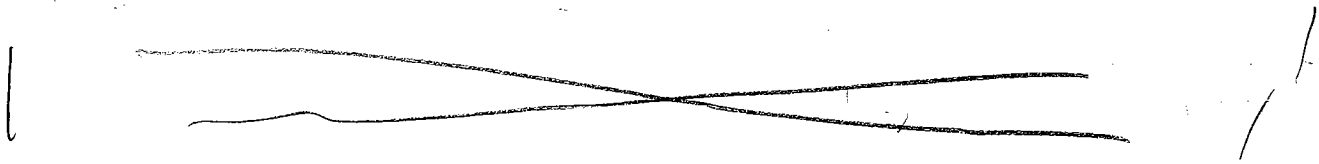

++++++++++++++++++++++++++++++++++++++++++++++++++++++++

**Simoneau, Margaret A**

**From:** Lubas, William (CDER)
**Sent:** Friday, March 28, 2003 12:33 PM
**To:** Michael C Elia (E-mail)
**Cc:** Parks, Mary H; Mele, Joy D; Orloff, David G; Haffer, Andrew; Mercier, Jennifer L; Simoneau, Margaret A; Sahlroot, Jon T
**Subject:** RE: Proposed labeling changes for ZOCOR

Dear Dr. Elia,

Zocor
ated label Revis

I have attached proposed labeling changes with reference to the NDA19-766/S-058 submission

Sincerely,
William Lubas MD-PhD

49 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_X_ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Administrative-* 19-766
SOSB

**Simoneau, Margaret A**

**From:** Lubas, William (CDER)
**Sent:** Thursday, March 27, 2003 9:42 AM
**To:** Mele, Joy D; Parks, Mary H; Orloff, David G; Sahlroot, Jon T; Simoneau, Margaret A
**Cc:** Haffer, Andrew
**Subject:** RE: Latest version of ZOCOR label for today's meeting

Hi,
I have attached the latest version of the label so that we can all be working from the same copy during today's meeting.

I tried to incorporate most of your suggestions, please let me know at the meeting if I missed anything.

Thanks,

Zocor
ated label Revis

Bill

**Simoneau, Margaret A**

**From:** Elia, Michael C [michael_elia@merck.com]
**nt:** Thursday, March 27, 2003 3:32 PM
**:** 'Lubas, William (CDER)'
**c:** 'Parks, Mary H'; 'Mele, Joy D'; 'simoneaum@cder.fda.gov'; Elia, Michael C
**Subject:** RE: NDA 19-766/S-058: Zocor Heart Protection Study - Information Requ est

**Importance:** High

Dr. Lubas, a short while after sending you the note below, I received a response from Oxford on the discontinuation rates. I will paraphrase the
relevant information here.

The definition of stopping treatment due to an adverse event is as follows:
anyone stopping due to muscle or liver enzyme abnormalities, muscle symptoms
or, if not taking a non-study statin, then if any symptom or diagnosis was
given as the reason for stopping, that reason was used.

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Please let me know if you have any further questions.

Thanks,
Mike

-----Original Message-----
From: Elia, Michael C
nt: Thursday, March 27, 2003 1:28 PM
: 'Lubas, William (CDER)'
Cc: Parks, Mary H; Mele, Joy D; Elia, Michael C;
'simoneaum@cder.fda.gov'
Subject: RE: NDA 19-766/S-058: Zocor Heart Protection Study -

Information Requ est
Importance: High

Dr. Lubas, below I've attached our responses to the questions you raised
st week. Note that Oxford needs another few days to provide the
formation that will allow you to verify the discontinuation rates.

Please let me know if we can be of any further assistance.

Thanks,
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Asst: Ms. Patricia Antell, 484-344-2313

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**Importance:** High


Lubas2a.doc


HPS sites.xls

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## Simoneau, Margaret A

**From:** Mercier, Jennifer L
**Sent:** Monday, March 17, 2003 10:46 AM
**To:** Simoneau, Margaret A
**Subject:** RE: ZOCOR HPS sNDA - MS Word version of proposed labeling

I do not need to attend, but could you please forward me the revised label in order for the Press Office to start working on a press release in order for it to be cleared by the time of approval.

Thanks,

Jen

301-594-5477 Revised 3/18/03

-----Original Message-----
From: Simoneau, Margaret A
Sent: Monday, March 17, 2003 8:50 AM
To: Mercier, Jennifer L
Cc: Galliers, Enid M; Johnson, Kati
Subject: FW: ZOCOR HPS sNDA - MS Word version of proposed labeling
Importance: High

Jennifer,

Follow-up info request for NDA 19-766 Zocor-S-058. There is an internal labeling meeting scheduled for March 24th at 3 pm if you'd like to attend.

Thanks,
Margaret

-----Original Message-----
From: Elia, Michael C [mailto:michael_elia@merck.com]
Sent: Tuesday, March 04, 2003 3:22 PM
To: 'lubasw@cder.fda.gov'
Cc: 'simoneaum@cder.fda.gov'; 'mele@cder.fda.gov'; Elia, Michael C
Subject: ZOCOR HPS sNDA - MS Word version of proposed labeling
Importance: High

Dr. Lubas:

Attached below please find two MS Word documents containing the (a) clean running text and (b) annotated versions of the proposed labeling for the Zocor Heart Protection Study. These documents were used to generate the PDF documents provided in the Jan 31, 2003 submisson to FDA.

Margaret:

In looking over the Jan 31, 2003 electronic submission, please note that the cover letter refers to a MS Word version of the labeling (clean running text) that is provided with that archival submission. It's called Proposed.doc and it's contained in the labeling subfolder. Given this, is necessary that we provide the MS Word version of the annotated labeling in a new archival submission or will this email suffice?

## Simoneau, Margaret A

**From:** Elia, Michael C [michael_elia@merck.com]
**Sent:** Monday, March 17, 2003 2:57 PM
**To:** 'MELE@cder.fda.gov'
**Cc:** 'nevius@cder.fda.gov'; 'sahlroott@cder.fda.gov'; Elia, Michael C; 'simoneaum@cder.fda.gov'

**Importance:** High

HPSRand140303.doc | Biometricsarticle pt 1.doc | biometricsarticle pt 2.doc

Joy, as we discussed briefly today, I'm attaching below Dr. Collins' response to your inquiry about the minimization algorithm used in the randomization of patients in HPS. He also provided a paper by Stuart Pocock
that Rory indicates is more directly relevant to the computerized methods
that Oxford used than the White & Freedman paper.

Per your request, I will set up a phone call with one or more of our statisticians to discuss with you their perspective on the use of the minimization algorithm in studies with large numbers (e.g., 20,000) of patients such as HPS.

Thanks,
Mike

<<HPSRand140303.doc>> <<Biometricsarticle pt 1.doc>> <biometricsarticle pt 2.doc>>

Michael C. Elia, PhD, DABT
Regulatory Affairs
Merck Research Laboratories
PO Box 4, BLA-20
West Point, PA 19486
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Fax 484-344-2516
E-mail: michael_elia@merck.com
Asst: Ms. Patricia Antell, 484-344-2313

# Heart Protection Study: Random allocation of study treatment using minimisation procedures to help ensure good balance

## Rationale for using minimisation even in large-scale trials

In controlled clinical trials, there are usually several prognostic factors known or thought to influence the patient's risk of events and their response to treatment. A serious imbalance between the treatment groups with regard to factors of prognostic importance can have serious implications for the unbiased assessment of the study treatment. Even in a large study, chance imbalances may occur that make interpretation difficult: for example, imbalances in baseline features among the 4,500 patients in the AMIS trial of aspirin post-MI were associated with a misleadingly unpromising result.[1] One method used to help achieve balance with respect to prognostic factors involves simple random treatment assignment within various strata. But, whilst reasonably good balance can be achieved with stratification on a limited number of prognostic variables, this may not be the case when balance is required across a large number of factors (e.g. four prognostic factors each at three levels yields 3 x 3 x 3 x 3 = 81 strata).[2,3] Indeed, it has been shown that the probability of material imbalance with simple random allocation within strata increases rapidly towards that of unstratified assignment as the number of strata increases (see Pocock and Simon: attached).

The pre-specified aim of HPS was to assess the effects of study treatment allocation on outcome reliably within a wide range of different categories of high-risk patient.[4] Minimisation was, therefore, used since it has been shown to provide good balance within a large number of different strata (age in 7 x sex in 2 x cholesterol in 6 x blood pressure in 3 x CHD in 5 x CVD in 4 x PVD in 4 x diabetes in 4 x smoking in 3 x ethnicity in 5 = 1,209,600 strata in HPS). As a consequence, for example, there was good balance between simvastatin versus placebo not only among all 6000 diabetic patients who were randomised in HPS, but also among diabetic patients without previous coronary or other vascular disease who presented with below average cholesterol levels.[5,6] (With respect to those factors that were not included in the minimisation algorithm, allocation between treatment groups would be as expected with simple random allocation, except that the balance for any factor that is associated with a factor included in the algorithm should also be improved.[2])

## Central allocation avoids predictability of the next treatment assignment

A major consideration in all treatment assignment procedures in trials is to ensure that the investigator entering a patient cannot predict in advance what the treatment assignment will be, since this might influence their decision to enter the patient and so bias the treatment comparison.[7,8] In HPS, patients were randomised by clinic nurses telephoning the coordinating centre to provide relevant details about eligibility that were recorded directly onto the coordinating centre computer. The computer then allocated the study treatment (i.e. active simvastatin plus active vitamins; active simvastatin plus placebo vitamins; placebo simvastatin plus active vitamins; or placebo simvastatin plus placebo vitamins) for that patient using a minimization algorithm. The algorithm aimed to minimise any differences in these "minimisation"

characteristics between the 4 possible treatment combinations by allocating the patient to the treatment group that would minimise any differences in the assignment "score" (using an algorithm shown to have the best statistical properties[2]). So, *for any particular order of patients*, treatment assignment would be deterministic, except – in the minority of cases (~8%) – when the treatment groups had equal scores. (Analogously, of course, treatment assignment according to a list previously generated from random numbers would also be deterministic for any particular order of patients.) But, this process would still involve random allocation of the study treatment among **all** of the participants since they were entered from a large number of clinics by staff who were unaware of the previous treatment allocations, of the characteristics of those patients who had already been randomised, and of the minimisation algorithm being used.[2,3,7] In this respect, what matters when using either a minimisation algorithm or an allocation sequence based on random numbers in ensuring proper randomisation is that the allocated treatment cannot be predicted prior to entry into the trial (which it could not be in HPS).[8]

There were 69 participating clinics in HPS and the treatment allocation was partially blocked within each clinic (i.e. "clinic" was not included in the minimisation algorithm). Randomisation packs were dispatched to the clinics in cases containing 5 packs of each of the 4 treatment combinations. All packs in the case currently being used were considered available for allocation and then, when only one pack in that case remained, all the packs in the next case also become available for allocation. In this way, any possibility of foreknowledge by people entering patients of the next pack to be allocated was avoided. (Moreover, since the active and placebo treatments looked identical, study nurses would not have been able to determine the treatments remaining in the current case by inspecting the contents of the packs.)

**Previous experience with minimisation procedures**

As is evident from the HPS data, the minimisation procedure has resulted in excellent balance between the treatment groups within a large number of strata.[5,6] The value of minimisation techniques to provide well-balanced random allocation of treatment within clinical trials has been considered in a number of papers by leading statisticians (see, for example, referenced papers by White and Freedman; Pocock and Simon [attached]; Armitage). These methods have also been used by a wide range of investigative groups in a number of other large-scale trials that have been subject to successful regulatory review, or will shortly be the subject of such review (e.g. ISIS trials in acute MI,[9] PROGRESS trial of blood pressure lowering therapy;[10] ASCOT trial of cholesterol lowering therapy,[11] and the ongoing ADVANCE trial of blood glucose lowering). The appropriateness of using minimisation procedures to help ensure balanced randomisation of treatment within large-scale clinical trials has also been discussed, and agreed, previously with representatives of FDA (such as Dr Robert Temple).

**Some relevant references**


1. Aspirin Myocardial Infarction Study (AMIS) Research Group. AMIS: a randomized controlled trial of aspirin in persons recovered from myocardial infarction. JAMA 1980; 243: 661-9.

2. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975; 31: 103-15 (attached).

3. White SJ, Freedman LS. Allocation of patients to treatment groups in a controlled clinical study. Br J Cancer 1978; 37: 849-57.

4. MRC/BHF Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering therapy and of antioxidant vitamin supplementation in a wide range of patients at increased risk of coronary heart disease death: early safety and efficacy experience. Eur Heart J 1999; 20: 725–41.

5. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360; 7–22.

6. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes and 14,573 other high-risk individuals: a randomised placebo-controlled trial. Lancet 2003 (submitted).

7. Armitage P. The role of randomization in clinical trials. Stat Med 1982; 1: 345-52.

8. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995; 273: 408-12.

9. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988; ii: 349-360.

10. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 2001; 358:1033–41.

11. Sever PS, Dahlöf B, Poulter NR, et al. The prevention of coronary and stroke events with atorvastatin in hypertensive subjects with average or below average cholesterol levels. The Anglo-Scandinavian Cardiac Outcomes Trial: Lipid Lowering Arm (ASCOT: LLA). Lancet 2003 (in press).

## Simoneau, Margaret A

**From:** Haffer, Andrew
**Sent:** Tuesday, March 11, 2003 11:29 AM
**To:** Simoneau, Margaret A
**Cc:** Hankin, Joan E
**Subject:** HPS for Zocor

Hi Peggy,

We received a draft television ad for review from Merck for Zocor. Merck said they plan to get approval for the HPS (Heart Protection Study) for Zocor shortly (19-766/S-058).

Can you update us on the timeline for their approval (from your end) and let us know what labeling changes they will get as a result of this supplement.

Thanks,

Andy

## Simoneau, Margaret A

**From:** Elia, Michael C [michael_elia@merck.com]
**Sent:** Tuesday, March 11, 2003 11:11 AM
**To:** 'Lubas, William (CDER)'
**Cc:** Simoneau, Margaret A; Parks, Mary H; Elia, Michael C
**Subject:** NDA 19-766/S-058: Zocor Heart Protection Study - Information Request

**Importance:** High

Response for
DA on liver prob

Dr. Lubas,

We forwarded your questions to Dr. Jane Armitage at Oxford University since she has access to the individual patient data (Merck remains blinded to these data). Attached below is the response from Oxford, with some more detail on the two patients reported as having hepatitis considered possibly drug-related. One was allocated to simvastatin, the other to placebo.

Dr. Armitage does not address one of the points you raised, namely the statement made in Section 9.5 about bilirubin not rising together with transaminases when the latter are increased by simvastatin. This is because the statement is not based on data from HPS, but rather the totality of our xperience with simvastatin. Therefore, Dr. Jonathan Tobert (Merck) rovided the following:

The warnings section of the label is specific to transaminases. Clinically significant increases in bilirubin are extremely uncommon during therapy with simvastatin, unless symptomatic hepatitis occurs. However, as in HPS and other studies, such cases are probably not caused by simvastatin. For example, in 4S there were two cases of nonviral hepatitis in the placebo group and one in the simvastatin group.

Symptomatic hepatitis and indeed hepatic failure without any identifiable cause occur occasionally in the absence of therapy with a statin, so that inability to find another cause does not necessarily mean statin causation. (Such cases may be caused by a virus yet to be identified, or a toxin not revealed to the treating physician, such as an acetaminophen overdose.) In the single case in HPS of a patient allocated to simvastatin with hepatitis considered possibly drug-related, the pattern of asymptomatic elevated transaminases after 18 months, then hepatic failure 9 months after stopping simvastatin is not the pattern of drug-induced hepatitis. Known patotoxins usually produce symptomatic hepatitis within a few weeks on eatment, not nine months after stopping treatment.

Please let me know if you have any additional questions.

# NDA 19-766/S-058: Zocor Heart Protection Study - Information Request

## Response to Dr Lubas' questions about liver problems reported during HPS

**Two cases of hepatitis reported (before unblinding) as possibly due to simvastatin during HPS**

There were two cases of hepatitis reported as believed due to study simvastatin treatment. Patient 100826 is described in the CSR, he developed abnormal liver function tests about 18 months after randomisation into HPS and stopped study simvastatin at that time. His liver function tests deteriorated despite stopping simvastatin and they remained abnormal until about 9 months later when he developed acute hepatic failure. He made a full recovery and liver histology at the time of his illness suggested a viral aetiology although no specific virus was identified on serology. Patient 710290 is the patient referred to in the CSR as the other hepatitis on placebo. He was admitted to hospital with hepato-renal failure about 3.5 years after randomisation. This was initially attributed to simvastatin and reported prior to unblinding of treatment allocation. Subsequently he was found to have septicaemia which was thought to be the underlying cause of the hepato-renal failure. This patient made a full recovery.

**Additional cases of liver problems reported during follow-up**

During HPS there were 9 cases of "hepatitis unspecified", 1 chronic hepatitis, 1 hepatic failure, 16 cirrhosis/chronic liver disease, 8 liver biopsies and 16 with unspecified liver problems reported. None of these reports was believed to be due to treatment either by the patient, the managing doctor or the coordinating centre clinician coding these events (in the context of the available blood results).

Further information was sought routinely about all liver biopsies (to exclude cancer) but not routinely about reports of "hepatitis unspecified", cirrhosis/chronic liver disease or "liver problems unspecified" if there was no reason to believe that the event was attributed to treatment. Additional information is available about some of these reported events because of follow-up of other events in the same individuals (see table).

**Routine monitoring of ALT but not bilirubin**

The liver function test alanine transaminase (ALT) was measured routinely at each clinic visit in all patients continuing on their study simvastatin or placebo tablets, but bilirubin was not routinely measured.

**Routine stopping of study treatment with abnormal liver function tests**

A pre-specified algorithm was followed to recall patients whose ALT was abnormal during follow-up and to stop the study simvastatin or placebo tablets either temporarily or permanently according to this algorithm, (or if other liver function tests were considered to be abnormal, by a study clinician or a managing doctor). The most common reason for stopping study simvastatin or placebo tablets as a result of the algorithm was when the ALT remained above 1.5 times the upper limit of normal (>67 IU/l in the HPS laboratory) after at least 6 weeks without study treatment. Hence patients with liver problems would typically have their study tablets stopped routinely as a result of abnormal liver function tests.

**Conclusion**

As Dr Lubas points out there is overlap between the cases and the 41 patients are almost equally divided between those allocated statin and those allocated placebo (20 simvastatin

versus 21 placebo). Moreover, looking at the information in the table there is no evidence to suggest that simvastatin was causing any of the reported liver problems, and for the majority of reports, there is some other explanation for the liver abnormalities or they were transient. In addition, the timing and biopsy results of the one patient allocated simvastatin who developed a severe hepatitis make a viral aetiology more likely than simvastatin as the underlying cause.

**Table showing details of patients in whom li[illegible]ms were reported.**

| ID | T | DI H | Day | Type of event | Comment |
|---|---|---|---|---|---|
| 100826 | 1 | | 874 | hepatitis unspecified, liver failure | See CSR. This patient was well at the time of his final follow-up in Aug 01 (see also below*) |
| 102180 | 3 | | 1404 | liver biopsy cirrhosis/chronic liver disease | Attributed to alcohol abuse |
| 102876 | 1 | | 300 | liver biopsy | Biopsy showed fatty liver with haemosiderosis |
| 121701 | 1 | | 390<br>1492<br>1522 | cirrhosis/chronic liver disease | Study treatment was stopped in 1997<br>Liver biopsy in May 00 suggested cirrhosis was secondary to autoimmune hepatitis |
| 160341 | 3 | | 1857<br>1959<br>2017 | liver problem unspecified<br>cirrhosis/chronic liver disease | Liver biopsy showed cirrhosis secondary to biliary disease. Stopped study treatment in 1996 as was being followed by telephone |
| 161144 | 3 | | 1327 | hepatitis unspecified | No further information but liver function tests normal in Jun 00 |
| 201711 | 3 | | 106 | liver problem unspecified | Not on study treatment at the time, no further information, liver function tests normal by the time of next follow-up |
| 211264 | 3 | | 88 | liver problem unspecified | Liver biopsy shows chronic hepatitis unknown cause, later dies of ovarian cancer |
| 232077 | 4 | | 1484 | cirrhosis/chronic liver disease | Died of intestinal obstruction but also had cirrhosis preterminally of unknown cause |
| 241072 | 3 | | 719 | liver problem unspecified | No further information, but normal liver function tests by Feb 98 |
| 242256 | 1 | | 182 | liver problem unspecified | No further information but normal liver function by Jan 97 |
| 262878 | 4 | | 1265 | liver biopsy | Liver biopsy consistent with severe right heart |

| | | | | |
|---|---|---|---|---|
| 290153 | 2 | 250 | liver problem unspecified | failure, treated for heart failure and improved. |
| 291807 | 4 | 1135 | liver problem unspecified | No further information but later develops heart failure |
| 292612 | 3 | 1248 | hepatitis unspecified | Stopped treatment because of persistently raised ALT, information from GP that it was probably alcohol induced |
| 330103 | 2 | 2143 | liver biopsy | No further information but not on study treatment at the time |
| 330637 | 2 | 1201 | hepatitis unspecified | Biopsy showed fatty liver |
| 331089 | 2 | 1980 | cirrhosis/chronic liver disease | No further information but continued treatment |
| 332005 | 1 | 1094 | liver problem unspecified | Died following amputation with several problems including liver disease |
| 340384 | 3 | 1871 | liver failure | Not on study treatment at time, no further information |
| 371094 | 3 | 1087 | liver problem unspecified | Never took study treatment, believed secondary to alcohol |
| 372199 | 4 | 828 | liver problem unspecified | Lymphoma diagnosed at lymph node biopsy Feb 99 |
| 391785 | 2 | 357 | liver problem unspecified | Complicating pneumonia and off study treatment at the time |
| 430516 | 4 | 1469 | hepatitis unspecified | Had liver metastases from unknown primary cancer |
| 441125 | 2 | 1381 | liver problem unspecified | Hepatitis believed secondary to verapamil, improved when it was stopped |
| 450274 | 4 | 1248 | cirrhosis/chronic liver disease | No further information but not on treatment at the time |
| 510131 | 3 | 415 | liver problem unspecified | Alcoholic liver disease, stopped treatment because of persistently elevated ALT |
| 541319 | 3 | 1298 | chronic hepatitis | Congestive cardiac failure at same time, no further information |
| | | | | Confirmed on liver |

| | | | | |
|---|---|---|---|---|
| | | | | biopsy, study treatment stopped Jun 99 because of persistent elevation of ALT |
| 611912 | 4 | 1064 | liver biopsy | Normal result, had been concern about metastases from colon cancer |
| 620194 | 3 | 1080 | hepatitis unspecified | Alcoholic hepatitis |
| 660398 | 4 | 604 | hepatitis unspecified | Only other information is congestive cardiac failure a few months before |
| 661522 | 2 | 1942 | liver biopsy | Showed fatty liver thought secondary to diabetes |
| 690733 | 3 | 718 | liver problem unspecified | Obstructive jaundice due to gall stone |
| 710290 | 2 | 1315 | hepatitis unspecified | See CSR: reported as SAE due to treatment later believed due to septicaemia |
| 730117 | 2 | 636 | hepatitis unspecified | No further information but liver function normal afterwards |
| 780583 | 4 | 434 | liver problem unspecified | Due to gallstones |
| 781733 | 4 | 984 | liver biopsy | Showed fatty liver, on methotrexate for rheumatoid arthritis |
| 800093 | 1 | 1653 | liver problem unspecified | Pancreatic cancer diagnosed shortly after |
| 820461 | 4 | 1262 | hepatitis unspecified | No other information, liver function normal by Jan 00 |
| 820962 | 4 | 416 | liver biopsy | Gallstones and lymphoma |
| 851170 | 3 | 823 | cirrhosis/chronic liver disease | Believed secondary to alcohol intake, stopped study treatment July 98 because of persistent elevation of ALT. |

* This patient was well at his final attendance at the HPS clinic in [redacted] and no cause for his liver failure was ever found. The reason for stopping the study tablets was "abnormal liver or muscle enzymes" which related to his liver failure [redacted] and remained the reason at his final follow-up) whereas he also chose to stop his vitamin or placebo capsules and so this was recorded as "patient's wishes".

Thanks,
Mike

-----Original Message-----
From: Lubas, William (CDER) [mailto:LubasW@cder.fda.gov]
Sent: Tuesday, March 04, 2003 4:20 PM
To: Michael C Elia (E-mail)
Cc: Simoneau, Margaret A; Parks, Mary H
Subject: RE: HPS Information request about LFTs/hepatitis/liver failure

Hi,

I noticed there are 10 cases with unspecified hepatits (?hepatitis?), one with chronic hepatitis 1, 16 with cirrhosis/chronic liver disease, 8 with liver biopsy, 2 with liver failure and 16 with liver problem unspecified in the AE dataset.

| PID | Tx | Days Hosp | Rel_ Day | RepTerm | AE Date |
|---|---|---|---|---|---|
| | 1 | | 874 | hepatits unspecified | |
| | 1 | | 874 | liver failure | |
| | 3 | | 1404 | liver biopsy | |
| | 3 | | 1404 | cirrhosis/chronic liver disease | |
| | 1 | | 300 | liver biopsy | |
| | 1 | | 390 | cirrhosis/chronic liver disease | |
| | 1 | | 1492 | cirrhosis/chronic liver disease | |
| | 1 | | 1522 | cirrhosis/chronic liver disease | |
| | 3 | | 1857 | liver problem unspecified | |
| | 3 | | 1959 | cirrhosis/chronic liver disease | |
| | 3 | | 2017 | cirrhosis/chronic liver disease | |
| | 3 | | 1327 | hepatits unspecified | |
| | 3 | | 106 | liver problem unspecified | |
| | 3 | | 88 | liver problem unspecified | |
| | 4 | | 1484 | cirrhosis/chronic liver disease | |
| | 3 | | 719 | liver problem unspecified | |
| | 1 | | 182 | liver problem unspecified | |
| | 4 | | 1265 | liver biopsy | |
| | 2 | | 250 | liver problem unspecified | |
| | 4 | | 1135 | liver problem unspecified | |

| | | |
|---|---|---|
| 3 | 1248 | hepatits unspecified |
| 2 | 2143 | liver biopsy |
| 2 | 1201 | hepatits unspecified |
| 2 | 1980 | cirrhosis/chronic liver disease |
| 1 | 1094 | liver problem unspecified |
| 3 | 1871 | liver failure |
| 3 | 1087 | liver problem unspecified |
| 4 | 828 | liver problem unspecified |
| 2 | 357 | liver problem unspecified |
| 4 | 1469 | hepatits unspecified |
| 2 | 1381 | liver problem unspecified |
| 4 | 1248 | cirrhosis/chronic liver disease |
| 3 | 415 | liver problem unspecified |
| 3 | 1298 | chronic hepatitis |
| 4 | 1064 | liver biopsy |
| 3 | 1080 | hepatits unspecified |
| 4 | 604 | hepatits unspecified |
| 2 | 1942 | liver biopsy |
| 3 | 718 | liver problem unspecified |
| 2 | 1315 | hepatits unspecified |
| 2 | 636 | hepatits unspecified |
| 4 | 434 | liver problem unspecified |
| 4 | 984 | liver biopsy |
| 1 | 1653 | liver problem unspecified |
| 4 | 1262 | hepatits unspecified |
| 4 | 416 | liver biopsy |
| 3 | 823 | cirrhosis/chronic liver disease |
| 3 | 836 | cirrhosis/chronic liver disease |
| 3 | 963 | cirrhosis/chronic liver disease |
| 3 | 983 | cirrhosis/chronic liver disease |
| 3 | 997 | cirrhosis/chronic liver disease |
| 3 | 1026 | cirrhosis/chronic liver disease |
| 3 | 1060 | cirrhosis/chronic liver disease |

All of these were considered serious according to the dataset with most

patients hospitalized for at least some time.

Clearly some of these cases overlapped but they represented 41 different patients almost equally split on statin and placebo (20 on simvastatin, 21
n placebo).

But I could only find the one narrative on pt 100826 in the serious drug-related AE narratives section 11.1.
Did you submit the information on the other patients in another part of the
submission?

Under Section 9.5 you mention there were 2 cases of hepatitis one in each
treatment group. I guess one was pt 100826, but which pt do you mean to refer to in the placebo group? Why weren't the other cases of serious hepatic disease described in more detail in the discussion? Only 9 pts completed the statin protocol out of these 41 patients so the cases must have been serious enough to stop the study statin.

Under Section 9.5 page 176 you mention that "simvastatin does not produce
increases in bilirubin together with raised transaminases..." Do you have
any bilirubin data? I could not find it in the LAB datasets.
Clearly pt 100826, who had a bilirubin of 459IU/L and transaminases > 1000IU/L would be an exception?

It is now over 5 years since the last AST recorded for pt 100826 (682IU/L on
[redacted] in the narrative on pg 185 of section 11.1. Do you know if there
ver was an etiology identified for the hepatitis? It looks from the LAB taset that his ALT normalized by [redacted] (40.2IU/L day 1534) and he continued on vitamins until day 2183 when he stopped because of "abnormal
liver or muscle enzymes" and "patient's wishes" according to the DISPOS database. I can't find any abnormal LFT's at this time (ALT = 24.39 on day
2392). Do you have any further follow up on this pt?

Thanks for you help,
William Lubas



WorldSecure Server <cder.fda.gov>" made the following annotations on 03/11/03 11:08:11

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[INFO] -- Access Manager:
This message was sent by Merck across the Internet in encrypted format
and was successfully decrypted, unless otherwise noted.

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**Simoneau, Margaret A**

**From:** Lubas, William (CDER)
**Sent:** Tuesday, March 04, 2003 4:20 PM
**To:** Michael C Elia (E-mail)
**Cc:** Simoneau, Margaret A; Parks, Mary H
**Subject:** RE: HPS Information request about LFTs/hepatitis/liver failure

Hi,

I noticed there are 10 cases with unspecified hepatits (?hepatitis?), one with chronic hepatitis 1, 16 with cirrhosis/chronic liver disease, 8 with liver biopsy, 2 with liver failure and 16 with liver problem unspecified in the AE dataset.

| PID | Tx | Days sp | Rel_ Day | RepTerm | AE Date |
|---|---|---|---|---|---|
| 100826 | 1 | | 874 | hepatits unspecified | |
| 100826 | 1 | | 874 | liver failure | |
| 102180 | 3 | | 1404 | liver biopsy | |
| 102180 | 3 | | 1404 | cirrhosis/chronic liver disease | |
| 102876 | 1 | | 300 | liver biopsy | |
| 121701 | 1 | | 390 | cirrhosis/chronic liver disease | |
| 121701 | 1 | | 1492 | cirrhosis/chronic liver disease | |
| 121701 | 1 | | 1522 | cirrhosis/chronic liver disease | |
| 160341 | 3 | | 1857 | liver problem unspecified | |
| 160341 | 3 | | 1959 | cirrhosis/chronic liver disease | |
| 160341 | 3 | | 2017 | cirrhosis/chronic liver disease | |
| 201144 | 3 | | 1327 | hepatits unspecified | |
| 201711 | 3 | | 106 | liver problem unspecified | |
| 211264 | 3 | | 88 | liver problem unspecified | |
| 232077 | 4 | | 1484 | cirrhosis/chronic liver disease | |
| 241072 | 3 | | 719 | liver problem unspecified | |
| 242256 | 1 | | 182 | liver problem unspecified | |
| 262878 | 4 | | 1265 | liver biopsy | |
| 290153 | 2 | | 250 | liver problem unspecified | |
| 291807 | 4 | | 1135 | liver problem unspecified | |
| 292612 | 3 | | 1248 | hepatits unspecified | |
| 330103 | 2 | | 2143 | liver biopsy | |
| 330637 | 2 | | 1201 | hepatits unspecified | |
| 331089 | 2 | | 1980 | cirrhosis/chronic liver disease | |
| 332005 | 1 | | 1094 | liver problem unspecified | |
| 340384 | 3 | | 1871 | liver failure | |
| 371094 | 3 | | 1087 | liver problem unspecified | |
| 372199 | 4 | | 828 | liver problem unspecified | |
| 391785 | 2 | | 357 | liver problem unspecified | |
| 430516 | 4 | | 1469 | hepatits unspecified | |
| 441125 | 2 | | 1381 | liver problem unspecified | |
| 450274 | 4 | | 1248 | cirrhosis/chronic liver disease | |
| 510131 | 3 | | 415 | liver problem unspecified | |
| 511319 | 3 | | 1298 | chronic hepatitis | |
| 611912 | 4 | | 1064 | liver biopsy | |
| 620194 | 3 | | 1080 | hepatits unspecified | |

| | | | |
|---|---|---|---|
| 660398 | 4 | 604 | hepatits unspecified |
| 661522 | 2 | 1942 | liver biopsy |
| 690733 | 3 | 718 | liver problem unspecified |
| 710290 | 2 | 1315 | hepatits unspecified |
| 0117 | 2 | 636 | hepatits unspecified |
| 80583 | 4 | 434 | liver problem unspecified |
| 781733 | 4 | 984 | liver biopsy |
| 800093 | 1 | 1653 | liver problem unspecified |
| 820461 | 4 | 1262 | hepatits unspecified |
| 820962 | 4 | 416 | liver biopsy |
| 851170 | 3 | 823 | cirrhosis/chronic liver disease |
| 851170 | 3 | 836 | cirrhosis/chronic liver disease |
| 851170 | 3 | 963 | cirrhosis/chronic liver disease |
| 851170 | 3 | 983 | cirrhosis/chronic liver disease |
| 851170 | 3 | 997 | cirrhosis/chronic liver disease |
| 851170 | 3 | 1026 | cirrhosis/chronic liver disease |
| 851170 | 3 | 1060 | cirrhosis/chronic liver disease |

All of these were considered serious according to the dataset with most patients hospitalized for at least some time.

Clearly some of these cases overlapped but they represented 41 different patients almost equally split on statin and placebo (20 on simvastatin, 21 on placebo).

But I could only find the one narrative on pt 100826 in the serious drug-related AE narratives section 11.1. Did you submit the information on the other patients in another part of the submission?

ader Section 9.5 you mention there were 2 cases of hepatitis one in each treatment group. I guess one was pt 100826, but which pt do you mean to refer to in the placebo group? Why weren't the other cases of serious hepatic disease described in more detail in the discussion? Only 9 pts completed the statin protocol out of these 41 patients so the cases must have been serious enough to stop the study statin.

Under Section 9.5 page 176 you mention that "simvastatin does not produce increases in bilirubin together with raised transaminases..." Do you have any bilirubin data? I could not find it in the LAB datasets.
Clearly pt 100826, who had a bilirubin of 459IU/L and transaminases > 1000IU/L would be an exception?

It is now over 5 years since the last AST recorded for pt 100826 (682IU/L on ——— a the narrative on pg 185 of section 11.1. Do you know if there ever was an etiology identified for the hepatitis? It looks from the LAB dataset that his ALT normalized b ——— 40.2IU/L day 1534) and he continued on vitamins until day 2183 when he stopped because of "abnormal liver or muscle enzymes" and "patient's wishes" according to the DISPOS database. I can't find any abnormal LFT's at this time (ALT = 24.39 on day 2392). Do you have any further follow up on this pt?

Thanks for you help,
William Lubas

## Simoneau, Margaret A

**From:** Mele, Joy D
**Sent:** Wednesday, February 19, 2003 7:01 AM
**To:** Simoneau, Margaret A; Parks, Mary H; Lubas, William (CDER); Sahlroot, Jon T
**Subject:** RE: Re: F/up to 2/11/03 status mtg for Zocor-058 (HPS)

Peggy,
Reassessing where I am with this NDA, I think that March 3 and 5th are too early to be discussing labeling - the first challenge will be to make the March 7th deadline - then I know I'll need another week to look at the labeling which I think needs a lot of changes. We may need a couple of internal meetings to discuss labeling later in the month before talking to Merck.
Thanks,
Joy

-----Original Message-----
**From:** Simoneau, Margaret A
**Sent:** Thursday, February 13, 2003 3:03 PM
**To:** Parks, Mary H; Lubas, William (CDER); Sahlroot, Jon T; Mele, Joy D
**Subject:** Re: F/up to 2/11/03 status mtg for Zocor-058 (HPS)

Everyone,

I apologize for not being at the status meeting on Tuesday but just wanted to let everyone know that I've scheduled an internal labeling meeting for March 3 and a tenative t-con with Merck on March 5th. The primary reviews are due in DFS by March 7, 2003. Please let me know if you anticipate any problems with the proposed meetings.

Thanks

Margaret Simoneau, M.S., R.Ph.
DA/CDER/HFD-510
01-827-6411
simoneaum@cder.fda.gov

## Simoneau, Margaret A

**From:** Elia, Michael C [michael_elia@merck.com]
**Sent:** Friday, February 07, 2003 5:16 PM
**To:** 'lubasw@cder.fda.gov'
**Cc:** 'mele@cder.fda.gov'; 'simoneaum@cder.fda.gov'; Elia, Michael C
**Subject:** RE: Update on Information Requests

Dr. Lubas,

Regarding item 2 below, I just received confirmation that the randomization values were not sent out by Oxford to anyone (i.e., GPs, consultants, collaborators).

Mike

-----Original Message-----
From: Elia, Michael C
Sent: Friday, February 07, 2003 4:44 PM
To: 'lubasw@cder.fda.gov'
Cc: 'mele@cder.fda.gov'; 'simoneaum@cder.fda.gov'; Elia, Michael C
Subject: RE: Update on Information Requests

Dr. Lubas,

1. In response to your first question, yes, lipid data were collected prior to and after the run-in period in HPS to permit an indirect randomized comparison of outcomes in patients who had a large response to simvastatin versus those who had a small response (see also our 22 Nov 2002 response to FDA request for information on the run-in period). The Screening Visit data serve as the baseline values and the Randomization Visit data serve as the follow-up values for the analyses of patient responsiveness to simvastatin treatment. These lipid data were provided in Item 11 and can be found in the non-compressed SAS files, LABCHOL.xpt, LABHDL.xpt, LABLDL.xpt and LABTRIG.xpt. All of these files contain a phase variable, S=Screening, R=Randomization E=Early Recall and F=Follow-up. Please note that these datasets include all patients who were randomized. They do not include this information for non-randomized patients.

2. Concerning who had access to the lipid data, based on the protocol, at the Screening Visit, the patient's total cholesterol was measured using a office/bedside device, so this was available to the treating physician (and to Oxford). The blood samples from the Screening Visits were analyzed by the Central Lab facility for lipids and biochemistry analyses. Results of these analyses, including the full lipid profiles, were sent to the patient's GP. I'm not sure if the central lab results from the Randomization Visit were sent to the GPs or not. We're checking into that

and will let you know ASAP.

3. Minimization algorithm for randomization. The algorithm used a number of factors based on SCREENING VISIT data only. With respect to lipids, the algorithm considered patients' total cholesterol in 6 categories (<3.5-4.0; 4.01-5.2; 5.21-6.0; 6.01-7.0; 7.01-7.8; or greater than or equal to 7.81 mmol/l). See also our 03 Feb 2003 response to FDA request for information on the algorithm.

4. Purpose of the active run-in period. As stated in our 22 Nov 2002 response to FDA request for information on the run-in period:

"The purpose of the active phase of the run-in period was primarily to permit an indirect randomized comparison of outcomes in patients who had a large response to simvastatin versus those who had a small response. Because responsiveness could be established during the run-in period, a randomized comparison was possible among good responders allocated to simvastatin versus good responders allocated to placebo, and similarly for poor responders. The risk reductions in good responders could then be compared to the risk reductions in poor responders. In contrast, previous trials have attempted to correlate lipid and lipoprotein changes in the active treatment group with cardiovascular outcomes. However, this type of analysis is uncontrolled and highly dependent on the model chosen. The innovative design adopted by the Oxford investigators avoids this problem, but it does raise the question of whether analyses of safety could be biased in favor of simvastatin due to withdrawal during the run-in period of patients who experienced adverse effects while receiving simvastatin prior to randomization."

I hope you find this information useful. Please let me know if you have any questions.

Mike

Michael C. Elia, PhD, DABT
Regulatory Affairs
Merck Research Laboratories
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West Point, PA 19486
Tel. 484-344-3180
Fax 484-344-2516
E-mail: michael_elia@merck.com
Asst: Ms. Patricia Antell, 484-344-2313

-----Original Message-----
From: Elia, Michael C
Sent: Thursday, February 06, 2003 7:36 PM
To: 'Lubas, William (CDER)'
Cc: Mele, Joy D; Elia, Michael C
Subject: RE: Update on Information Requests

Dr. Lubas, thanks for your note. I will let you know ASAP about providing
you with the detailed lipid data from the run-in period.

Thanks,
ike

-----Original Message-----
From: Lubas, William (CDER) [mailto:LubasW@cder.fda.gov]
Sent: Thursday, February 06, 2003 4:36 PM
To: 'Elia, Michael C'
Cc: Mele, Joy D
Subject: RE: Update on Information Requests

Hi,
I am not sure that I received that information I requested about the baseline LDL-cholesterol levels in the run in group. The 11/22 Dropout Data
Set only has Lab_Chol listed as Yes (<3.5mmol/l) or No (>) but gave no numerical data.

Were lipid profiles or total cholesterol determined both before and after
the Run In period but before randomization "to allow a prerandomization assessment of the LDL-lowering "responsiveness" of each individual"?

If so who had access to this information? (e.g. GP, collaborator, consultant
etc.) Can I see this numerical data set?

If not then were only baseline lipid levels before starting on simvastatin
sed in the original minimization protocol?

hen what was the point of the initial 6 weeks of active treatment?

To cull patients with potential adverse reactions to the drug who would be
more likely not to complete the trial?

I appreciate your help in clarifying this situation.

William Lubas
CDER/DMEDP

-----Original Message-----
From: Elia, Michael C [mailto:michael_elia@merck.com]
Sent: Wednesday, October 23, 2002 6:30 PM
To: 'LUBASW@CDER.FDA.GOV'
Cc: 'SIMONEAUM@CDER.FDA.GOV'
Subject: Update on Information Requests

Dr. Lubas,

Here's an update on your two outstanding information requests:

1. [redacted]. I expect to be able to
ovide
esponses to your questions via email or fax sometime tomorrow.

2. Heart Protection Study - Data on run-in period. We've received

from
Oxford data on patients that dropped out of the run-in period. Later this
week I hope to send you SAS XPT files for these patients, along with our
assessment of the impact of these dropouts on the results and
interpretation
for HPS.

Thanks,
Mike

Michael C. Elia, PhD, DABT
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PO Box 4, BLA-20
West Point, PA 19486
Tel. 484-344-3180
Fax 484-344-2516
E-mail: michael_elia@merck.com
Asst: Ms. Patricia Antell, 484-344-2313

## Simoneau, Margaret A

**From:** Elia, Michael C [michael_elia@merck.com]
**Sent:** Thursday, February 06, 2003 4:11 PM
**To:** 'Mele, Joy D'
**Cc:** Elia, Michael C; 'simoneaum@cder.fda.gov'
**Subject:** RE: database question

Joy, here's the procedure:

Patients who took a non-study statin and continued in the study can be identified by performing the following steps:

1. In the CONTHRP dataset (in Item 11), locate the T_CLASS variable field.
Filter for STATIN (represents non-study statin, STATINA (represents non-study atorvastatin), STATINC (represents non-study cerivastatin), STATINF (represents non-study fluvastatin), STATINP (represents non-study
pravastatin) and STATINS (represents non-study simvastatin). This will isolate all patients who took a non-study statin during the study.

2. In the EPDISCON dataset, locate the STSTATIN variable field. Patients
who have a "1" (yes) in the STSTATIN variable field are those that discontinued from the study because they started taking a non-study statin.

3. Finally, compare the patients identified in Step 1 with those identified
in Step 2. Patients common to both the Step 1 and Step 2 datasets can
disregarded since they represent patients that discontinued from the study
because they started taking a non-study statin. The remaining patients will
be the those that continued in the study while taking non-study statin.

Also, I was asked to clarify for you the meaning of SCSTATIN variable in the
EPDISCON dataset. This variable represents those patients who stopped capsules because they started a non-study statin. Capsules contain vitamin
or vitamin placebo. This variable does not automatically mean the patient
stopped simvastatin.

Thanks,
Mike

-----Original Message-----
From: Mele, Joy D [mailto:MELE@cder.fda.gov]
Sent: Thursday, February 06, 2003 3:35 PM
To: 'Elia, Michael C'
Subject: RE: database question

ke -
Thanks very much. I won't look at this until next week so no rush.
Joy

-----Original Message-----
From: Elia, Michael C [mailto:michael_elia@merck.com]
Sent: Thursday, February 06, 2003 1:11 PM
To: 'Mele, Joy D'
Cc: Elia, Michael C
Subject: RE: database question

Joy, it looks like we'll be able to help you directly with this one. One
can generate a list of pts that continued in the study on non-study statins
using the T_CLASS variable in the Item 11 CONTHRP file and comparing that to
the EPDISCON file. We will send you the logic and procedure for this later
today.

Mike

-----Original Message-----
From: Mele, Joy D [mailto:MELE@cder.fda.gov]
Sent: Wednesday, February 05, 2003 7:04 AM
To: 'Elia, Michael C'
Subject: RE: database question

Mike - It would be good if you can help me directly because I most likely
have similar questions as the review goes along. Thanks for your quick
reply. - Joy

-----Original Message-----
From: Elia, Michael C [mailto:michael_elia@merck.com]
Sent: Tuesday, February 04, 2003 5:02 PM
To: 'Mele, Joy D'
Subject: RE: database question

Joy, I have a call out to see if we can help you with this directly, or
whether we need to get Oxford involved. Will let you know as soon as
possible either way.

Thanks,
Mike

-----Original Message-----
From: Mele, Joy D [mailto:MELE@cder.fda.gov]
Sent: Tuesday, February 04, 2003 2:35 PM
To: 'Elia, Michael C'
Subject: database question

Mike,
I would like to identify those patients who took non-study statins. Some
of these patients would have discontinued for this reason -- these I can
identify with the variables STSTATIN and SCSTATIN on dataset EPDISCON. How
do I identify those patients that continued on study while taking non-study
statins (i.e. after the protocol amendment)?
Thanks for your help.
Joy (301-827-6376)

SCJ 050385

Michael C. Elia, Ph.D., DABT
Senior Director
Regulatory Affairs

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NDA SUPPL AMENDMENT

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February 3, 2003

David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II (CDER)

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Research Laboratories

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c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Orloff:

**NDA 19-766/S-058: ZOCOR™ (Simvastatin)**

**Response to FDA Request For Information**

Reference is made to the supplemental New Drug Application cited above for ZOCOR™ submitted as an electronic archive on June 18, 2002 by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. Reference is also made to the telephone conversation of January 24, 2003 between Ms. Joy Mele (FDA Statistical Reviewer) and Dr. Michael C. Elia (MRL), during which Ms. Mele requested details on the minimization algorithm and an example of the process used to randomize a hypothetical patient in the Heart Protection Study (HPS).

Merck is providing in Item 20 a memo from Dr. Jane Armitage, Clinical Trials Services Unit (CTSU), Oxford University with the information requested in the January 24 telephone conversation.

We hope that responses provided in this submission have adequately addressed the Agency's comments and requests.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 7.51, Symantec Corp., 2000) and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolic and Endocrine Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Margaret Simoneau, R.Ph., M.S., Senior Regulatory Project Manager, Division of Metabolic and Endocrine Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Michael C. Elia, Ph.D., DABT (484-344-3180) or, in my absence, to Edwin L. Hemwall, Ph.D. (484-344-2306).

Sincerely,

M. C. Elia

Michael C. Elia, Ph.D., DABT
Senior Director, Regulatory Affairs

Enclosure: CD

Federal Express # 1

Q://_bconroy/ZOCOR/NDA Letters/HPS/19766_HPS-response_mininm_algorithm.doc

Desk Copies: Margaret Simoneau, R.Ph., M.S.
Regulatory Project Manager (cover letter)
HFD-510, Room 14B-19
Federal Express #2

Michael C. Elia, Ph.D., DAB
Senior Director
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January 31, 2003

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David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products

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SEQ # (BL)
NDA SUPPL AMENDMENT

FEB 0 4

Dear Dr. Orloff:

**NDA 19-766/S-058: ZOCOR™ (Simvastatin) Heart Protection Study**

**Minor Amendment to a Pending Application**

Pursuant to Section 505(b) of the Food, Drug and Cosmetic Act, we submit, for the Agency's review and approval, an amendment to NDA 19-766/S-058.

As indicated on the attached Form FDA 356h, this minor amendment provides for changes in the ***Labeling*** Section of the approved New Drug Application for ZOCOR.

This amendment describes revisions incorporating minor numerical corrections to the Heart Protection Study (HPS) data, which do not affect the study results or conclusions. The data in the original draft labeling, submitted to FDA on 18-June-2002 in NDA 19-766/S-058, originated from a database frozen by Oxford in March 2002. Subsequent to this, updated data were derived from a database frozen by Oxford in May 2002 and analyzed (by Oxford) in June 2002 to support the Lancet publication (THE LANCET Vol 360, pp-7-22, July 6, 2002) which detailed the study. Merck provided FDA with individual patient datasets to support these changes on 23-Sep-2002.

The revised, annotated Package Circular shows all HPS labeling (from the original supplement as well as this amendment) with revision marks. The above-mentioned numerical corrections have also been shown in bold for review purposes only. Additional editorial changes are also shown with revision marks and annotated accordingly.

Please note that this revised draft labeling is based on the last approved circular (#782544X), which corresponds to NDA #19-766/S-056 (pediatric), approved by FDA on 18-Oct-2002. The last approved circular has not yet been printed. In contrast, the original HPS supplement (S-058, dated 18-Jun-2002) utilized the "last approved/approvable text as of April 2002" as the base document on which the HPS revisions were shown.

In summary, this amendment to a pending application updates the original HPS proposed labeling for consistency with the published manuscript and previously submitted datasets.

The Statement of Organization following this letter describes the sections contained in this application.

With this submission are the following items:

Labeling
I. Labeling history
II. Labeling text
    a. Proposed labeling text
    b. Currently used labeling text (#7825442)
    c. Last approved labeling text (#782544X)

Summary
I. Annotated package circular

Also included as an attachment to this cover is a memo from Dr. Jane Armitage, Clinical Trials Services Unit (CTSU), Oxford University that explains the differences between the Heart Protection Study (HPS) March Clinical Study Report and the Lancet Publication, (THE LANCET Vol 360, pp-7-22, July 6, 2002).

The Microsoft WORD version of the proposed labeling text is also supplied as PROPOSED.DOC within the labeling folder on the Compact Disk (CD) provided.

This supplemental application is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 7.51, Symantec Corp., 2000) and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolic and Endocrine Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Margaret Simoneau, R.Ph., M.S., Senior Regulatory Project Manager, Division of Metabolic and Endocrine Drug Products.

In accordance with the Prescription Drug User Fee Act of 1992 (PDUFA) and reauthorized in the Food and Drug Administration Modernization Act of 1997 (FDAMA) and the Prescription Drug User Fee Amendments of 2002 (PDUFA III), as indicated in the attached Form 3397, no user fee is required for this supplemental application.

Merck & Co., Inc. is requesting a categorical exclusion for the requirements to prepare an Environmental Assessment under 21 CFR 25.31(*a*). This supplement meets the requirements of a categorical exclusion under 21 CFR 25.31(*a*) because it will not increase the use of the active moiety. To the best of the firm's knowledge no extraordinary circumstances exist in regard to this action.

We consider the filing of this supplemental New Drug Application to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this supplemental application should be directed to Michael C. Elia, Ph.D., DABT (484-344-3180) or, in my absence, to Edwin L. Hemwall, Ph.D. (484-344-2306).

Sincerely,

for

Michael C. Elia, Ph.D., DABT
Senior Director, Regulatory Affairs

Enclosure: CD
Attachment
Federal Express # 1

Q:_BConroy\ZOCOR\NDA Letters\HPS\changes_to_label_amend.doc

Desk Copies: Margaret Simoneau, R.Ph., M.S., Regulatory Project Manager (cover letter)
And Attachment
HFD-510, Room 14B-19
Federal Express #2

**Reasons for minor differences between the Heart Protection Study March CSR data and the Lancet publication.**

There are 3 main areas where on-going coding and checking of HPS data led to changes between the numbers of events in the CSR and the Lancet publication (but not to any material changes in the findings).

**1. Deaths due to heart failure:** During 2000 the Chairman and Deputy Chairman of the HPS Steering Committee independently coded 50 deaths of HPS participants as a pre-specified check of the HPS coding procedures. As a result of this exercise, the coding rules for heart failure deaths were modified to ensure that such deaths considered to have an underlying cause of coronary heart disease were appropriately coded as coronary deaths. Otherwise, these heart failure deaths for which the underlying cause was not considered to be due to coronary disease (or was uncertain) were to be coded as unspecified heart failure and thus counted under 'other vascular' causes of death. Some deaths had already been coded before this modification to the rules, and such heart failure deaths were to be reviewed, prior to finalising the data, to ensure consistency of coding, and this was undertaken in April 2002. Sixty-one deaths previously included in "other vascular" causes were reviewed, blind to treatment allocation, independently by two CTSU clinicians and heart failure was attributed to coronary disease in 37. This is the main reason for the increase of 34 in coronary deaths and the decrease in 'other vascular' seen between the March CSR data and the published numbers. Continued receipt of information about cause of death from hospitals and health authorities also led to further coding of some deaths and small changes in other numbers and dates.

**2. Reasons for stopping medication:** As part of on-going data checking various categories of reasons for stopping medication were reviewed between March and May 2001. In particular these included the reasons of "elevated liver or muscle enzymes" (which could not be separated from the data recorded on the HPS follow-up form) and "muscle symptoms". Records from all these individuals were reviewed to allow stopping due to elevated liver enzymes (detected both from within the study and by other doctors) to be distinguished from stopping due to raised CK. Similarly to ensure that myopathy and myalgia codes had been used consistently, forms with these codes were also reviewed. This led to some minor coding changes and small changes to the numbers of people recorded as having stopped study treatment due to raised ALT, CK or muscle symptoms.

**3. Ongoing confirmation and coding of events:** Further information about events of interest continued to be received and reviewed after the data freeze on which the CSR is based. Such information from GPs, health authorities or medical records can lead both to events no longer being counted (if, for example, a patient's report of a heart attack is not confirmed according to the HPS diagnostic criteria for MI) and to new events being reported from sources other than the patient and entered into the database. The net overall effect of this is minor with an increase of just 17 major vascular events (<0.5% of the total) between the March CSR data and the published data, but there will be small differences in the numbers of events across the whole range of different endpoints.

In addition, three further types of change led to minor differences in some data files (but no discernible effects on analyses). First, during data checking, large differences identified between actual visit date and "expected" date for particular follow-up numbers were reviewed. Corrections to some of these dates led to some changes in the visit number. Secondly, an error was detected in the value of the data field recorded about continuation of study simvastatin from certain Early Recall

forms. Extensive checks of all forms that could possibly have been affected revealed 145 errors on such forms which were all corrected with direct reference to the Early Recall Form. This accounts for the majority of differences between March and June data in the compliance data file, but it had no discernible effect on estimated compliance in different treatment groups. The third type of minor change resulted from applying further range checks to data for waist and hip measurements which excluded anomalous values (e.g. where inches were probably recorded instead of centimeters), and helped detect and correct trailing blanks which led to a few changes in hip and waist measurements, but again this had no material effect on any analyses.

Jane Armitage
9 October 2002

## STATEMENT OF ORGANIZATION

### NDA 19-766: ZOCOR™ (Simvastatin)
### Amendment to Pending Application

This submission contains the following paper and/or electronic information:

| ITEM(s) | DESCRIPTION | Contents on Archival CD | Archival Copy | Paper Review Copies |
|---|---|---|---|---|
| 1 | Administrative Data containing Archival CD | Yes | Blue Binder (1 volume) | No |
| 2 | Labeling* | Yes | No | No |
| 3 | Synopsis of Application | Yes | No | No |

*The WORD version of the proposed labeling text is provided on archival CD.

**TOTAL VOLUMES: 1**

## Simoneau, Margaret A

**From:** Parks, Mary H
**Sent:** Wednesday, January 15, 2003 4:17 PM
**To:** Lubas, William (CDER); Mele, Joy D
**Cc:** Simoneau, Margaret A; Orloff, David G
**Subject:** HPS

Joy and Bill

FYI-

I just got a call from Mike Elia at Merck and he asked about submitting a revised label to reflect the HPS publication that came out late last year. He assured me that the datasets reviewed in that publication were sent to this sNDA already and have been in house for some time. If this revised label is indeed what they want to take to the table for negotiations and we already have the data to review I told him it would make more sense to send in the new proposed label so that we don't waste time reviewing and commenting on an outdated label.

Mary

Michael C. Elia, Ph.D., DABT
Senior Director
Regulatory Affairs

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November 22, 2002

MERCK
Research Laboratories

David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Orloff:

**NDA 19-766/S-058: ZOCOR™ (Simvastatin)**

**Response to FDA Request For Information**

Reference is made to the supplemental New Drug Application cited above for ZOCOR™ submitted as an electronic archive on June 18, 2002 by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. Reference is also made to the telephone conversation of August 1, 2002 between Dr. William Lubas (FDA Medical Reviewer) and Dr. Michael C. Elia (MRL) during which Dr. Lubas requested detailed datasets for non-randomized patients in the Heart Protection Study (HPS) due to concerns about possible bias introduced into the safety analyses by the use of an active run-in period prior to randomization.

Merck is providing in Item 11 detailed datasets for non-randomized patients as requested in the telephone conversation of August 1, 2002. In addition, provided in Item 20 is a memo from Jonathan Tobert, M.D. (MRL) responding to Dr. Lubas' question regarding run-in period.

The Statement of Organization following this letter describes the sections contained in this application.

We hope that responses provided in this submission have adequately addressed the Agency's comments and requests.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the amendment. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 600MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 7.5.1, Symantec Corp., 2000) and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolic and Endocrine Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Margaret Simoneau, R.Ph., M.S., Senior Regulatory Project Manager, Division of Metabolic and Endocrine Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Michael C. Elia, Ph.D., DABT (484-344-3180) or, in my absence, to Edwin L. Hemwall, Ph.D. (484-344-2306).

Sincerely,

M. C. Elia

Michael C. Elia, Ph.D., DABT
Senior Director, Regulatory Affairs

Enclosure: CD

Federal Express # 1

Q:_BConroy\ZOCOR\NDA Letters\HPS\19766_HPS_resp_run-in-period.doc

Desk Copies: Margaret Simoneau, R.Ph., M.S.
Regulatory Project Manager (cover letter)
HFD-510, Room 14B-19
Federal Express #2

Dr. William Lubas, FDA medical reviewer (cover letter)
HFD-510, Room 14B-19
Federal Express #2

Dr. Joy Mele, FDA statistical reviewer (cover letter)
HFD-510, Room 14B-19
Federal Express #2

## STATEMENT OF ORGANIZATION

## NDA 19-766/S-058: ZOCOR™ (Simvastatin)

This submission contains the following paper and/or electronic information:

| ITEM(s) | DESCRIPTION | Contents on Archival CD | Review Aids | Archival Copy/ Paper Review Copies |
|---|---|---|---|---|
| 1, 20 | Administrative Data containing Archival CD* | Yes | No | Blue Binder (1 volume each) |
| 11 | Case Report Tabulations | Yes | No | No |

**TOTAL VOLUMES: 1**

*The Archival CD is contained in the Blue Binder

## Simoneau, Margaret A

**From:** Elia, Michael C [michael_elia@merck.com]
**Sent:** Wednesday, October 23, 2002 6:30 PM
**To:** 'LUBASW@CDER.FDA.GOV'
**Cc:** 'SIMONEAUM@CDER.FDA.GOV'
**Subject:** Update on Information Requests

Dr. Lubas,

Here's an update on your two outstanding information requests:

1. Recent label change to include information on [redacted] I expect to be able to provide
responses to your questions via email or fax sometime tomorrow.

2. Heart Protection Study - Data on run-in period. We've received from
Oxford data on patients that dropped out of the run-in period. Later this
week I hope to send you SAS XPT files for these patients, along with our assessment of the impact of these dropouts on the results and interpretation
of HPS.

Thanks,
Mike

chael C. Elia, PhD, DABT
egulatory Affairs
Merck Research Laboratories
PO Box 4, BLA-20
West Point, PA 19486
Tel. 484-344-3180
Fax 484-344-2516
E-mail: michael_elia@merck.com
Asst: Ms. Patricia Antell, 484-344-2313

Michael C. Elia, Ph.D., DABT
Senior Director
Regulatory Affairs

ORIGINAL

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215 652 5000
Fax 484 344 2516
Email: michael_elia@merck.com

MERCK
Research Laboratories

September 23, 2002

David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products

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c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

SE1 05 8 (BM)

NDA SUPPL AMENDMENT

Dear Dr. Orloff:

**NDA 19-766/S-058: ZOCOR™ (Simvastatin)**

**Response to FDA Request For Information**

Reference is made to the supplemental New Drug Application cited above for ZOCOR™ submitted as an electronic archive on June 18, 2002 by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. This supplement included proposed draft labeling based on the results of Protocol 102, The Heart Protection Study (HPS) performed by the Clinical Trials Service Unit (CTSU) of Oxford University. Reference is also made to the memorandum dated July 5, 2002 from Ms. Joy Mele (FDA Statistical Reviewer), requesting additional information. Reference is also made to the email correspondence dated July 22, 2002 from Ms. Mele to Dr. Michael C. Elia (MRL) responding to questions Merck had posed to the FDA on behalf of Oxford pertaining to the EPDISCON file (Item 11 SAS Transport File) and to a July 24, 2002 email from Dr. Elia to Ms. Mele requesting clarification to additional questions from Oxford. Additional reference is made to the July 25, 2002 telephone conversation between Dr. William Lubas (FDA Medical Reviewer) and Dr. Elia responding to the July 24, 2002 email.

Reference is also made to the email of August 9, 2002 from Dr. Elia to Ms. Mele, Dr. Mary Parks, Dr. Lubas, and Ms. Margaret Simoneau (FDA) providing a sample of the proposed compressed Item 11 datasets. Reference is made to a telephone conversation between Dr. Rory Collins (Principal Investigator and Professor, University of Oxford) and Dr. David Orloff (FDA) on July 12, 2002 and to a telephone conversation between Dr. Collins and Ms. Mele on July 15, 2002. Reference is also made to the August 2, 2002 letter from Dr. Collins to Ms. Mele, which is being supplied in this response.

As requested in the FDA memorandum dated July 5, 2002 compressed datasets for Item 11 from the updated June 21, 2002 database freeze (used to support the *Lancet* paper) and the revised original endpoint data sets are enclosed in Item 11 of this submission.

In Item 20, Merck is providing updated Clinical Study Report (CSR) tables and figures based on the updated June 21, 2002 database freeze. Our response to Dr. Lubas's request of August 1, 2002 for additional information regarding CSR Table 8 (non-randomized patients) will be forthcoming. That information will be submitted under separate cover as soon as it is available.

The Statement of Organization following this letter describes the sections contained in this application.

We hope that responses provided in this submission have adequately addressed the Agency's comments and requests.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs*. As an attachment to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the amendment. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 650MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 7.5.1, Symantec Corp., 2000) and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolic and Endocrine Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Margaret Simoneau, R.Ph., M.S., Senior Regulatory Project Manager, Division of Metabolic and Endocrine Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Michael C. Elia, Ph.D., DABT (484-344-3180) or, in my absence, to Edwin L. Hemwall, Ph.D. (484-344-2306).

Sincerely,

M. C. Elia

Michael C. Elia, Ph.D., DABT
Senior Director, Regulatory Affairs

Enclosure

Hand Deliver

Q:_BConroy\ZOCOR\NDA Letters\dataset response 4_.doc

Desk Copies: Margaret Simoneau, R.Ph., M.S.
Regulatory Project Manager (cover letter)
HFD-510, Room 14B-19
Federal Express #1

Dr. William Lubas, FDA medical reviewer (cover letter)
HFD-510, Room 14B-19
Federal Express #1

Dr. Joy Mele, FDA statistical reviewer (cover letter)
HFD-510, Room 14B-19
Federal Express #1

Michael C. Elia, Ph.D., DABT
Senior Director
Regulatory Affairs

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P.O. Box 4
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Tel 484 344 3180
215 652 5000
Fax 484 344 2516
Email: michael_elia@merck.com

September 16, 2002

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David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II (CDER)

MERCK
Research Laboratories

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Orloff:

SE1 058 BM
NDA SUPPL AMENDMENT

**NDA 19-766/S-058: ZOCOR™ (Simvastatin)**

**Response to FDA Request For Information**

Reference is made to the supplemental New Drug Application cited above for ZOCOR™ submitted as an electronic archive on June 18, 2002. Reference is also made to the phone conversation of Wednesday, August 28, 2002 between Ms. Susan Nolt, Sr. Regulatory Coordinator, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., and Dr. William Lubas, Medical Reviewer, FDA regarding that supplemental New Drug Application. During this conversation Dr. Lubas requested information pertaining to the Heart Protection Study (HPS) sNDA and the July 2002 Lancet article.

With this submission, we are providing Merck's responses to the August 28, 2002 telephone conversation cited above.

**Responses to Dr. Lubas's Questions Pertaining to HPS**

1. **Response to question regarding discrepancies between myopathies reported in the publication and the CSR:**

MRL has always considered myopathy to be unexplained muscle pain or weakness accompanied by CK > 10X ULN. Rhabdomyolysis is defined (somewhat arbitrarily) as a subset of these patients with CK 10,000 IU (>40X ULN when the ULN is 250 as in many laboratories including Oxford).

The published paper includes a few additional cases not in the CSR, in both the simvastatin and placebo groups. In essence, the CSR excluded doubtful cases from the myopathy total count while the paper included them. Thus, discrepancies between the CSR and the published paper are due to the interpretation of cases that were complex and/or had missing information (as indicated in the CSR). Also, in the case of one patient in the placebo group information became available to the Oxford investigators after the CSR was written. Details are provided below.

Patient identification numbers of the patients with myopathy counted in both Table 4 of the HPS publication and Table 34 of the CSR are in Table 1 below. Additional information on these patients is in Table 35 of the CSR. Narratives for patients 501632, 820587, 860579, and 370023 are in Sections 11.1.2 and 11.1.3 of the CSR. WAES reports for patients 292322 and 240160 are attached.

**Table 1**

**Patients with Myopathy Counted in Both the Publication and CSR Identification Numbers**

| | Simvastatin Group Patient ID | Placebo Group Patient ID |
|---|---|---|
| **Rhabdomyolysis** | 501632 | 240160 |
| | 292322 | 370023* |
| | 820587 | |
| | 860579 | |
| **No Rhabdomyolysis** | 230040 | 450323 |
| | 642338 | |
| | 411421 | |

*Considered rhabdomyolysis in publication, but myopathy in CSR

Identification numbers of patients causing discrepancies in the myopathy patient counts between Table 4 of the HPS publication and Table 34 of the CSR are in Table 2 below.

**Table 2**

**Discrepancies in Myopathies Between the Publication and CSR Patient Identification Numbers**

| | Simvastatin Group Patient ID | Placebo Group Patient ID |
|---|---|---|
| **Rhabdomyolysis** | 160673 | 370023* |
| | | 120389 |
| **No Rhabdomyolysis** | 350564 | |
| | 631279 | |

*Considered rhabdomyolysis in publication, but myopathy in CSR.

Reasons for the discrepancies between the publication and CSR follow:

**Rhabdomyolysis**

**Simvastatin Group**

160673 This patient had an episode counted as rhabdomyolysis in the publication, but not in the CSR. The episode was not counted as a rhabdomyolysis in the CSR because it was recorded only on a post mortem report and was not considered due to study drug. The patient was hospitalized for an aortic aneurysm repair, and "following complications of that operation he returned to theatre for urgent fasciotomies. He developed acute renal failure secondary to rhabdomyolysis". He did not recover and died. The cause of death is coded as coronary heart disease.

This adverse event was not reported to CTSU as drug-related and there is no implication in the post-mortem report that it was thought due to study treatment. Furthermore, it is not known whether he was taking study treatment during this episode.

**Placebo Group**

370023 This patient was counted as having myopathy in both the publication and CSR. The peak CK value was reported as >9000 IU/L, so this was not considered rhabdomyolysis in the CSR based on the definition of muscle symptoms with CK>10,000 IU/L. However, this was counted as a rhabdomyolysis in the publication.

120389 This rhabdomyolysis was counted in the publication, but not in the CSR. This additional rhabdomyolysis was picked up from information supplied about the patient's death. It had not been entered into the database at the time the CSR, was written, although the elevated CK was counted among the cases of elevated CK in Table 37 of the CSR.

**No Rhabdomyolysis**

**Simvastatin Group**

350564 This patient had muscle symptoms and an elevated CK, but not at the same time. He had muscle pain and weakness following a colectomy for colon cancer, and a CK elevation at the next scheduled visit 2 months later, by which time he was asymptomatic. Although this was counted as a myopathy in the publication, it was not in the CSR because the muscle symptoms did not coincide with the CK elevation.

631279 This case was counted as a myopathy in the publication but not in the CSR because this patient's symptoms may well have been due factors other than simvastatin. This patient had a myocardial infarction treated with tissue plasminogen activator (tPA) and followed by coronary angioplasty. The day after the procedure, he developed a deep vein thrombosis and pain in the thigh, and was also noted to have a raised CK (6800 IU/L). The managing physicians believed this may have been due to multiple fat emboli. He was managed with anti-coagulation and recovered. He stopped study treatment temporarily around this time. He later restarted study treatment, which he continued until just before the end of the study without any problems. This suggests that the symptoms and raised CK were probably caused by fat emboli and/or deep vein thrombosis, as opposed to simvastatin.

**2. Response to question about patients on erythromycin and verapamil:**

Per CSR Table 35, the 2 patients on erythromycin were 501632 and 820587. The 2 patients on verapamil were 230040 and 411421.

**3. Response to question about patients with ALT>3X ULN:** The number of patients in each treatment group with consecutive ALT elevations >3x ULN is at the end of CSR Table 38 (simvastatin: 21 ( 0.21%) vs. placebo: 9 (0.09%). The number of patients in each treatment group with consecutive ALT elevations >3x ULN is at the end of CSR Table 38 (simvastatin: 21 ( 0.21%) vs. placebo: 9 (0.09%).

The number of patients discontinued due to abnormal liver enzymes is in CSR Table 9 (simvastatin: 41 ( 0.4%) vs. placebo: 32 (0.3%). The numbers of patients discontinued due to abnormal liver enzymes differ from those in the publication [simvastatin 48 (0.5%) vs placebo: 35 (0.3%)] because the publication was based on a database frozen subsequently to the one used for the CSR. Also, the numbers in the publication include patients discontinued due to both liver and muscle enzyme elevations in addition to those discontinued for liver enzyme elevations only. As described in CSR Section 8.2, discontinuations due to liver enzyme abnormalities resulted either from the application of the protocol-defined algorithm to liver function test abnormalities measured within the study (CSR Section 5.5.3), or from enzyme abnormalities measured outside the study.

We hope that responses provided in this submission have adequately addressed the Agency's comments and requests.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk CD Tape which contains the amendment. All documents requiring signatures for certifications are included as paper for archival purposes.

All of the information is contained on one CD Tape and is not more than 100MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolic and Endocrine Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Margaret Simoneau, R.Ph., M.S., Senior Regulatory Project Manager, Division of Metabolic and Endocrine Drug Products.

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Questions concerning this submission should be directed to Michael C. Elia, Ph.D., DABT (484-344-3180) or, in my absence, to Edwin L. Hemwall, Ph.D. (484-344-2306).

Sincerely,

M. C. Elia

Michael C. Elia, Ph.D., DABT
Senior Director, Regulatory Affairs

Enclosure: CD

Federal Express # 1

Desk Copies: Margaret Simoneau, R.Ph., M.S.
Regulatory Project Manager (cover letter)
HFD-510, Room 14B-19
Federal Express #2

Q:_BConroy\ZOCOR\NDA Letters\19-766_resp to fda_Dr.Lubas.doc

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-766/S-058

Merck & Co., Inc.
Attention: Michael Elia, Ph.D., DABT
Senior Director, Regulatory Affairs
Sumneytown Pike, P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Elia:

Please refer to your pending efficacy submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zocor (simvastatin) Tablets.

We also refer to our acknowledgment letter dated July 1, 2002, that stated the drug review priority classification for this application would be determined at the filing meeting.

Upon further consideration of your application, we have concluded that this application should receive a standard review. The user fee goal date is April 19, 2003.

If you have any questions, call Margaret Simoneau, Regulatory Project Manager, at (301) 827-6411.

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/

Mary Parks
8/16/02 09:38:22 AM
for Dr. Orloff

**********
*** TX REPORT ***
**********

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| PGS. SENT | 3 |
| RESULT | OK |

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: August 16, 2002

Center for Drug Evaluation and Research
FDA

TO:

Name: Dr. Michael Elia

Fax No.: 484-344-2516

Phone No.: 484-344-3180

Location: Merck

Pages: 3 (including cover)

FROM:

Name: Margaret Simoneau

Fax No.: (301) 443-9282

Phone No.: (301) 827-6411

Location: FDA

**ROUTING AND TRANSMITTAL SLIP**

Date: August 13, 2002

| TO: (Name, office symbol, room number, building, Agency/Post) | Initials | Date |
|---|---|---|
| 1. Dr. Parks Fine | | 8/13 |
| 2. Enid Jackins * PLEASE note D's to Doc Info PAGES | | |
| 3. | | |
| 4. | | |
| 5. | | |

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| | Comment | | Investigate | | Signature |
| | Coordination | | Justify | | |

**REMARKS**

NAA 19-766/8-058

AD ltr e/r to notification

of Standard Review Priority

Note:

**DO NOT use this form as a RECORD of approvals, concurrences, disposals, clearances, and similar actions**

| FROM: (Name, org. symbol, Agency/Post) | Room No.—Bldg. |
|---|---|
| M. Simoneau | Phone No. 7611 |

5041-103 *U.S. GPO: 1996-404-763/40011 **OPTIONAL FORM 41 (Rev. 1-94)** Prescribed by GSA

## Simoneau, Margaret A

**From:** Mele, Joy D
**Sent:** Friday, August 16, 2002 11:43 AM
**To:** 'Elia, Michael C'
**Cc:** Mele, Joy D; Simoneau, Margaret A; Parks, Mary H; Lubas, William
**Subject:** RE: Zocor Heart Protection Study sNDA Filing

Mike,
I have taken a look at the dataset you sent and I have the following comments:

1. The documentation shows that the variable EXAMVALU will be converted to numeric. This was not done on the sample dataset - I assume it will be done for future datasets.
2. VISITNUM should also be converted to numeric.
3. What does the value of "E" represent for PHASE?
4. The EP datasets should include the same standard variables proposed for the other datasets.
5. We had discussed putting the lipids in one dataset since only a subset of the patients had values. Would you let me know why you decided against this?

In general, the proposal for the new datasets looks good to me. Dr. Lubas may have additional suggestions.

Joy Mele

301-827-6376

-----Original Message-----
From: Elia, Michael C [mailto:michael_elia@merck.com]
Sent: Monday, August 12, 2002 8:23 AM
To: 'mele@cder.fda.gov'; 'parksm@cder.fda.gov'; 'lubasw@cder.fda.gov'; 'simoneaum@cder.fda.gov'
Cc: Elia, Michael C
Subject: Zocor Heart Protection Study sNDA Filing
Importance: High

Resending, sorry if this is a duplicate!
Mike

> -----Original Message-----
> From: Elia, Michael C
> Sent: Monday, August 12, 2002 7:57 AM
> To: 'MELE@CDER.FDA.GOV'; 'PARKSM@CDER.FDA.GOV'; 'LUBASW@CDER.FDA.GOV';
> 'SIMONEAUM@CDER.FDA.GOV'
> Cc: Elia, Michael C
> Subject:
> Importance: High
>
>
> Mary and Joy,
>
> In follow up to my email sent Friday, 09 Aug, here I've provided you with
> information about how some of the various endpoint values will be revised
> when we use the updated data used in the Lancet Heart Protection Study
> paper (published 06 Jul). The "datapackage" file contains a summary

of
> the endpoint values in the original sNDA and those updated values used
to
> support the Lancet paper. The "USPC" file shows how the proposed
label
would change using the updated data. And the "clin data" file shows
examples of how the figures would look using the revised data.
>
> As you will see, the updated data used to support the Lancet paper
> represent small changes in the endpoint values that do not change our
> interpretation of the study results or the study conclusions. Thus,
we'd
> like to provide you with these revised data for your review, as they
> represent the most accurate set of information we have on HPS and
> ultimately would allow the label to be in numerical agreement with the
> Lancet paper.
>
> <<Datapackage.doc>> <<USPC Revised 09 Aug 2002
Final430.doc>>
> <<clin data pkg figs.doc>>
>
> I hope this information, together with the material sent in my 09 Aug
> email are sufficient to allow you to concur that the HPS sNDA should
be
> filed on or before 18 Aug. Pls let me know as soon as possible on
this
> point, and also whether you agree that we should use the updated data
to
> prepare the new statistical data files per our discussion with Joy.
>
> Thanks,
> Mike
>

Michael C. Elia, PhD, DABT
> Regulatory Affairs
> Merck Research Laboratories
> PO Box 4, BLA-20
> West Point, PA 19486
> Tel. 484-344-3180
> Fax 484-344-2516
> E-mail: michael_elia@merck.com
> Asst: Ms. Patricia Antell, 484-344-2313
>

## Simoneau, Margaret A

**From:** Elia, Michael C [michael_elia@merck.com]
**Sent:** Friday, August 09, 2002 11:04 AM
**To:** 'MELE@CDER.FDA.GOV'; 'PARKSM@CDER.FDA.GOV'; 'LUBASW@CDER.FDA.GOV'; 'SIMONEAUM@CDER.FDA.GOV'
**Cc:** Elia, Michael C; Chafart, Edward J.; Orfe, Daniel F.

**Importance:** High


Creat.zip


HPS Dataset Compression rules....

Joy,

Here's an update on where we stand with respect to regenerating the HPS datasets in the ways that would be most useful for the agency's review. We've discussed internally and with Oxford the best approach for generating the requested data. Based on the discussion that Ed Chafart, Dan Ofre and I had with you recently, we also sent a memo to Oxford that describes the planned "basic rules for compression" that we've asked Oxford to follow to generate the new data files. Using these rules, Ed produced a file for creatinine from the original Lab Chemistry SAS Transport file (decode notes included). Because Merck remains blinded to the individual patient data (held at Oxford), you'll notice that in the Creatinine file the treatment group=1 for all listings. Nevertheless, we hope you find this example useful to review to see if it meets your needs.

Also of interest, and as predicted, reformatting substantially reduced the file size:

* The original file was 21.8 MB in size
* After compression, the creatinine SAS Transport file is 4.8MB in size
* 22% of the original size.

Oxford is working with us to produce these new files over the course of this month, with delivery to FDA expected by 30 Aug 02. Although this is a couple of weeks after the agency's deadline for filing, Merck and Oxford are committed to providing you with the requested information in a timely manner. As we discussed, we expect the FDA will agree that our committment, and the information provided here describing our plans, are sufficient to allow the agency to affirm that the HPS sNDA will be filed for review.

Another important question for which we'd like your feedback concerns which frozen file to use to generate the new data files. As we've discussed, our original submission contains data from a March data freeze. However, the recently published Lancet paper on HPS used a data from a freeze that was done a couple of months later, and contains some updated information

that
results in slightly different numerical values for some endpoints, but
does
not alter the study conclusions or interpretation. Oxford can provide
either. Based on our previous discussions it seems that you'd prefer to
ve the updated data from the later data freeze for your review. Since
'd like in the end to have our HPS labeling match the numbers in the
Lancet paper we also believe this is the best way to proceed.
Separately, I
will provide you with a summary listing of the differences in the
endpoint
values between the two frozen files that affect our proposed labeling, a
copy of our new proposed labeling that reflects the updated numbers, and
a
set of revised tables and figures based on the later data freeze.

<<Creat.zip>> <<HPS Dataset Compression rules.doc>>

Although I haven't yet had a chance to follow up with Dr. Lubas on this,
Merck would be happy to provide Dr. Lubas with a loaner laptop loaded
with
the new HPS data if that would be helpful in facilitating his review
(i.e.,
to avoid delays in downloading large files from a central server to his
desktop computer).

Thanks,
Mike

Michael C. Elia, PhD, DABT
Regulatory Affairs
Merck Research Laboratories
) Box 4, BLA-20
st Point, PA 19486
el. 484-344-3180
Fax 484-344-2516
E-mail: michael_elia@merck.com
Asst: Ms. Patricia Antell, 484-344-2313

**Simoneau, Margaret A**

**From:** Kelly, Sharon L
**nt:** Thursday, August 01, 2002 10:49 AM
**:** Simoneau, Margaret A
**Subject:** Filing Meeting 19-766 s-058

Hi Peggy;

There is an Environmental Assessment for the Heart Protection Study - Protocol 102; and there is no Item 4, CMC info.

There are no CMC filing issues for this Supplement.

Sharon

DEPARTMENT OF HEALTH & HUMAN SERVICES

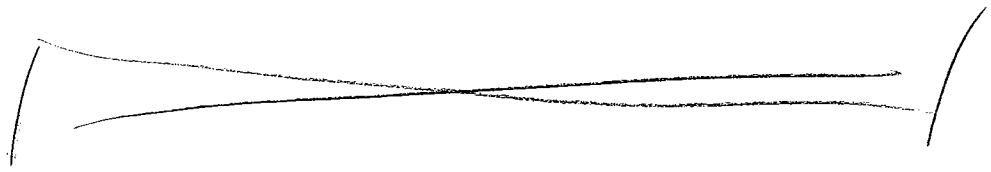
Public Health Service

Food and Drug Administration
Rockville, MD 20857

**TRANSMITTED BY FACSIMILE**

Kathryn A. Roberts,
Regulatory Director, Office of Medical/Legal,
Merck & Co., Inc.
U.S. Human Health
P.O. Box 1000
North Wales, PA 19454-1099

RE: **NDA 19-766 ZOCOR® (simvastatin) Tablets**



- Proposed peer-reviewed journal reprint to be disseminated:

  Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. *Lancet.* 2002; 360: 7-22.

Dear Ms. Roberts:

On July 11, 2002, the Food and Drug Administration received your submission of materials pursuant to 21 CFR Part 99, "Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices."

We are currently reviewing your entire submission and will notify you whether or not it meets the applicable provisions of the regulation.

Kathyrn A. Roberts,
Merck & Co., Inc.
NDA 19-766

July 22, 2002

If you have any questions, you may contact the undersigned at the Division of Drug Marketing, Advertising, and Communications, HFD-42, 5600 Fishers Lane, Rockville, MD 20857, or by facsimile at (301) 594-6759.

Sincerely,

*{See appended electronic signature page}*

Elaine J. Hu, R.Ph.
Regulatory Review Officer
Evidence Review Group
Division of Drug Marketing,
Advertising, and Communications

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/

Elaine J. Hu
7/22/02 03:51:06 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

# REQUEST FOR CONSULTATION

TO: William Wirks
~~Anne Pariser~~, Medical Officer
Division of Cardio-Renal Drug Products (HFD-110)
N Room 14B-04

FROM: **Elaine J. Hu**, Regulatory Review Officer,
Division of Drug Marketing, Advertising, and
Communications (HFD-42)
(301) 827-3888

| DATE: | IND NO.: | NDA NO.: | TYPE OF DOCUMENT: | DATE OF DOCUMENT: |
|---|---|---|---|---|
| **July 18, 2002** | | **19-766** | ~~validation~~ ~~documents~~ | **July 10, 2002** |

| NAME OF DRUG: | PRIORITY CONSIDERATION: | CLASSIFICATION OF DRUG: | DESIRED COMPLETION DATE: |
|---|---|---|---|
| **ZOCOR (simvastatin)** | **HIGH** | | **August 23, 2002** |

NAME OF FIRM: **Merck & Co., Inc.**

## REASON FOR REQUEST

### I. GENERAL

☐ NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY
☐ PRE--NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT
☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
X OTHER *(SPECIFY BELOW)*:
**Off-Label Submission**

### II. BIOMETRICS

| ISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
|---|---|
| PE A OR B NDA REVIEW<br>☐ END OF PHASE II MEETING<br>☐ CONTROLLED STUDIES<br>☐ PROTOCOL REVIEW<br>☐ OTHER: | ☐ CHEMISTRY REVIEW<br>☐ PHARMACOLOGY<br>☐ BIOPHARMACEUTICS<br>☐ OTHER: |

### III. BIOPHARMACEUTICS

☐ DISSOLUTION
☐ BIOAVAILABILTY STUDIES
☐ PHASE IV STUDIES
☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST

### IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISON RISK ANALYSIS

### V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

**COMMENTS/SPECIAL INSTRUCTIONS:**
**Dissemination of information on an unapproved/new use for Zocor.** RPM-SIMONEAU

| SIGNATURE OF REQUESTER: | METHOD OF DELIVERY (Check one): ☐ MAIL ☒ HAND |
|---|---|
| ATURE OF RECEIVER: | SIGNATURE OF DELIVERER: |

**Simoneau, Margaret A**

**From:** Hu, Elaine J
**Sent:** Tuesday, July 16, 2002 7:50 AM
**:** Pariser, Anne
**:** Burke, Laurie B; Simoneau, Margaret A; Miller, Catherine; Haffer, Andrew
**Subject:** ZOCOR Off-Label Use Submission

Hello Dr. Pariser,

This is to inform you that DDMAC received a submission from Merck for dissemination of information on an unapproved/new use for Zocor pursuant to 21 CFR Part 99.

The unapproved/new use is for Zocor in reducing

Merck certifies that they submitted an sNDA on June 18, 2002 to support these claims based on the Heart Protection Study.

I am in the process of putting together a formal consult to you and will send it out later this week. Please let me know if you have any questions when you receive the consult package.

Thanks and have a great day!
Elaine

Elaine J. Hu, R.Ph.,
Regulatory Review Officer,
Division of Drug Marketing, Advertising, and Communications
phone: (301) 827-3888
x: (301) 594-6771

## Simoneau, Margaret A

**From:** Elia, Michael C [michael_elia@merck.com]
**Sent:** Friday, July 05, 2002 11:28 AM
**To:** 'MELE@CDER.FDA.GOV'
**Cc:** 'SAHLROOTT@CDER.FDA.GOV'; 'LUBASW@CDER.FDA.GOV'; 'SIMONEAUM@CDER.FDA.GOV'; Elia, Michael C
**Subject:** RE: HPS data request

Joy, thanks for sending this detailed list. I will discuss this with the team and get back to you and Todd as soon as I can. As you might expect, many folks are taking today off, so it's unlikely that I'll be able to respond today; I'll let you know the status of our response early next week.

Thanks,
Mike

-----Original Message-----
From: Mele, Joy D [mailto:MELE@cder.fda.gov]
Sent: Friday, July 05, 2002 10:59 AM
To: 'michael_elia@merck.com'
Cc: Sahlroot, Jon T; Lubas, William; Mele, Joy D; Simoneau, Margaret A
Subject: HPS data request

Dr. Elia,
Please find attached a word document which describes the revised datasets that I need to proceed with my review of the Heart Protection Study. This request was discussed with the medical reviewer, Bill Lubas and includes his input.
I will be in the office today until about 2 and I will be on vacation all next week. Todd Sahlroot (Biometrics Team Leader) at 301-827-6387 will be available next week to address questions you may have regarding this request.
Thank you for your help.
Joy Mele

<<hps.data request.doc>>

======

"WorldSecure Server <cder.fda.gov>" made the following
annotations on 07/05/02 12:21:15

---

[INFO] -- Access Manager:
This message was sent by Merck across the Internet in encrypted format
and was successfully decrypted, unless otherwise noted.

==========
======

## Simoneau, Margaret A

**From:** Mele, Joy D
**Sent:** Friday, July 05, 2002 10:59 AM
**To:** 'michael_elia@merck.com'
**Cc:** Sahlroot, Jon T; Lubas, William; Mele, Joy D; Simoneau, Margaret A
**Subject:** HPS data request

Dr. Elia,

Please find attached a word document which describes the revised datasets that I need to proceed with my review of the Heart Protection Study. This request was discussed with the medical reviewer, Bill Lubas and includes his input.

I will be in the office today until about 2 and I will be on vacation all next week. Todd Sahlroot (Biometrics Team Leader) at 301-827-6387 will be available next week to address questions you may have regarding this request.

Thank you for your help.

Joy Mele

hps.data request.doc

**MEMORANDUM**

**DEPARTMENT OF HEALTH & HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

Date: July 5, 2002

Between: Michael C. Elia, Ph.D.
Senior Director
Regulatory Affairs
Merck Research Laboratories
Tel. (973) 781-3570
email michael_elia@merck.com

And: Joy D. Mele, M.S.
Statistician
FDA - CDER
Division of Biometrics 2, HFD-715
Parklawn Building, 10B06
5600 Fishers Lane
Rockville, MD 20857-1706
Tel. (301) 827-6376
FAX (301) 827-5875

Subject: Request for revised datasets (NDA 19766 SE1 058)

1. Please include a unique patient identifier on every dataset.
2. Extra observations are included in several datasets checked by this reviewer. These observations contain data inconsistent with the rest of the data on the dataset. For example, for dataset EPSUBGP, there are 20,538 observations when there should be 20,536 observations. The two extra observations contain values of [redacted] several variables and other data as well that is clearly incorrect.
3. The subgroup variables should be included in each endpoint dataset.
4. The endpoint datasets should include a treatment variable for vitamin use.
5. The stroke endpoint dataset should include a variable for ischemic vs. haemorrhagic stroke.
6. Endpoint datasets need to be provided for the following endpoints:
   MORTALITY (include a variable for cause of death)
   NON-CHD MORTALITY
   NON-FATAL MI
   REVASCULARIZATION PROCEDURES (include a variable for coronary vs. non-coronary procedure)
   HOSPITALIZATION FOR ANGINA
   PERIPHERAL MACROVASCULAR COMPLICATIONS OF DIABETES (include a variable for type of complication: peripheral revascularization procedure, lower limb amputation and leg ulcer)

7. The following additional subgroup variables (all measured at baseline) should be included in each endpoint dataset:
   HISTORY OF STROKE
   AGE AND BASELINE LIPIDS (mg/dL only) should be included as both categorical variables and continuous variables
   BASELINE HBA1C (continuous variable)
   METABOLIC SYNDROME
   SMOKING STATUS
   ALCOHOL INTAKE
   OBESITY
   BASELINE BMI (continuous variable)
   BASELINE DIASTOLIC PRESSURE (categorical and continuous variable)
   BASELINE SYSTOLIC PRESSURE (categorical and continuous variable)

8. Please provide a discontinuation dataset with the following variables:
   Unique Patient Identifier
   Site (STUDYNUM)
   AGE
   GENDER
   RACE
   Statin treatment variable
   Vitamin treatment variable
   Completer (Y/N)
   Date Randomized
   Date withdrawn from statin/statin placebo
   Date withdrawn from vitamin/ vitamin placebo
   Days on statin/statin placebo
   Days on vitamin/vitamin placebo
   Primary reason for withdrawal from statin/statin placebo
   Primary reason for withdrawal from vitamin/ vitamin placebo
   Secondary reason for withdrawal from statin/statin placebo
   Secondary reason for withdrawal from vitamin/ vitamin placebo
   Tertiary reason for withdrawal from statin/statin placebo
   Tertiary reason for withdrawal from vitamin/ vitamin placebo

   Note this dataset should contain one record per patient.

Please submit these datasets to the CDER electronic document room. Please call me at 301-827-6376 to discuss any questions or issues surrounding this request. Note that this request is made after a preliminary review of the data and the application. Additional requests may follow during the review process.

Joy D. Mele, M.S.
Mathematical Statistician

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-766/S-058

**PRIOR APPROVAL SUPPLEMENT**

Merck & Co., Inc.
Attention: Michael C. Elia, Ph.D., DABT
Senior Director, Regulatory Affairs
Sumneytown Pike, P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Elia:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

| | |
|---|---|
| Name of Drug Product: | Zocor (simvastatin) Tablets |
| NDA Number: | 19-766 |
| Supplement Number: | S-058 |
| Review Priority Classification: | Standard or Priority will be determined at Filing Meeting |
| Date of Supplement: | June 18, 2002 |
| Date of Receipt: | June 19, 2002 |

This supplement proposes to add additional information to various sections of the Package Insert from the Heart Protection Study (HPS) evaluating the effects on mortality and morbidity of Zocor in a wide range of patients at high risk of coronary heart disease.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 18, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 19, 2003.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6411.

Sincerely,

*{See appended electronic signature page}*

Margaret Simoneau, R.Ph.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/

Margaret Simoneau
7/1/02 11:37:56 AM

**Simoneau, Margaret A**

**From:** RCV_BUTLER@OCOFM.FDA.GOV
**Sent:** Thursday, June 20, 2002 5:06 PM
**To:** KACUBAA@CDER.FDA.GOV; LUTWAKV@CDER.FDA.GOV; WRIGHTM@CDER.FDA.GOV; KOZMAFORNARO@CDER.FDA.GOV; CROSSF@CDER.FDA.GOV; ZECCOLAA@CDER.FDA.GOV; CATTERSOND@CDER.FDA.GOV; KLUNKK@CDER.FDA.GOV; STRONGINB@CDER.FDA.GOV; HOLMESJ@CDER.FDA.GOV; ROBERTSK@CDER.FDA.GOV; YOKOYAMAJ@CDER.FDA.GOV; OLIVERK@CDER.FDA.GOV; BARNES@CDER.FDA.GOV; LESANE@CDER.FDA.GOV; MOODY@CDER.FDA.GOV; PEASE@CDER.FDA.GOV; CARTERL@CDER.FDA.GOV; BUEHLER@CDER.FDA.GOV; JANIP@CDER.FDA.GOV; MCDONALDZ@CDER.FDA.GOV; MORGENSTERN@CDER.FDA.GOV; ROEDERD@CDER.FDA.GOV; DAVID@CDER.FDA.GOV; HARDEMANS@CDER.FDA.GOV; MILLEM@CDER.FDA.GOV; NIGHSWANDER@CDER.FDA.GOV; PURVISJ@CDER.FDA.GOV; SCHUMAKER@CDER.FDA.GOV; BLAYR@CDER.FDA.GOV; CHEEVERJ@CDER.FDA.GOV; KUMMERERS@CDER.FDA.GOV; LANGE@CDER.FDA.GOV; MCCORTS@CDER.FDA.GOV; RHEEJ@CDER.FDA.GOV; COLLIERB@CDER.FDA.GOV; JOHNSONKA@CDER.FDA.GOV; WALSH@CDER.FDA.GOV
**Subject:** USER FEE PAYMENT & ARREARS LIST

**********FY 2002 USER FEE RATES**********

Effective January 16, 2002, applicants must send the full Fiscal Year 2002
application fee at the time of submission for fee liable applications and
supplements. The fees for Fiscal Year 2002, announced in the Federal Register
dated January 16, 2002, are:

Application/Clinical Data Required..... $ 313,320
Supplement/Clinical Data Required.....$ 156,660
Application/No Clinical Data Required..$ 156,660

An application should be accepted for filing if a fee is submitted even if the
amount of the fee is incorrect. The firm should be contacted and told to
promptly remit the balance (with the same user fee ID number). [Also alert the
user fee staff if this should occur.] As before, applications (except
pediatric supplements received after January 3, 2002) for which NO FEE has been
received by FDA within 5 days of the receipt date of the application (30 days
for pediatric supplements until July 1, 2002) should not be accepted for filing
per MAPP 6050.1. If you have questions, please contact the user fee staff.

NOTE: * denotes entries since last report

# 1 Page(s) Withheld

1 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Administrative* 19-766
5058

Michael C. Elia, Ph.D., DABT
Director
Regulatory Affairs

DESK COPY

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486
Tel 484 344 3180
215 652 5000
Fax 484 344 2516
Email: michael_elia@merck.com

June 18, 2002

David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

MERCK
Research Laboratories

Dear Dr. Orloff:

**NDA 19-766: ZOCOR™ Tablets (Simvastatin)**
**Supplemental New Drug Application: Request for Priority Review Status**

**Heart Protection Study – Protocol 102**

Reference is made to the approved NDA cited above for ZOCOR™ and to our pre-sNDA meeting of December 17, 2001. Pursuant to Section 505(b) of the Food, Drug and Cosmetic Act and in accordance with 506A(c)(1) of the Food and Drug Administration Modernization Act, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., submits for the Agency's review and approval, a supplement to NDA 19-766.

This application contains information from a large, multicenter, double-blind, placebo-controlled, randomized trial evaluating the effects on mortality and morbidity of ZOCOR™ in a wide range of patients at high risk of coronary heart disease (Protocol 102, *"A Randomized Study of the Effects on Mortality and Morbidity of HMG-CoA Reductase Inhibitors and of Antioxidant Vitamins in a Wide Range of People at High Risk of Coronary Heart Disease"*). Also known as the Heart Protection Study (HPS), this megatrial included 20,536 patients at high risk of coronary heart disease (CHD) randomized to simvastatin 40 mg vs. placebo for five years. In addition, all patients were randomized to compare antioxidant vitamin supplementation (vitamins E and C and beta-carotene) vs. placebo. Since the results of HPS showed that there was no effect of the vitamins on any study endpoint nor was there any interaction between simvastatin and the vitamins, our submission focuses on the efficacy and safety of simvastatin vs. placebo.

The results of the landmark Heart Protection Study provide unequivocal evidence of the benefits of simvastatin therapy on mortality, major coronary events and stroke in a wide array of patients at high risk of CHD events. Patients at high risk were defined as those with either diabetes, a history of stroke or other cerebrovascular disease, peripheral vessel disease, or existing coronary heart disease. Predefined subgroup analyses based predominantly on major vascular events (a composite endpoint experienced by over 4,600 patients, comprising non-fatal MI, CHD death, stroke or revascularization procedures) showed that simvastatin reduced risk *regardless of prior disease, age, gender or baseline LDL-C level.*

Based on the HPS results, we propose to revise and broaden the existing Coronary Heart Disease indication in the ZOCOR™ label to include

The demonstration by HPS that simvastatin significantly reduces the risk of major vascular events in patients: [redacted] represents beneficial effects not previously reported for simvastatin or any other lipid-modifying agent of any class.

The currently approved labeling for ZOCOR™ (and other lipid lowering therapies) includes the recommendations for use of lipid lowering drugs according to a patient's 10-year CHD risk and LDL-C level as specified by the current National Cholesterol Education Program (NCEP) Treatment Guidelines. For patients at highest risk, the recommendation is to initiate drug therapy if LDL-C $\geq$ 130 mg/dL; treatment of patients with LDL-C = 100-129 mg/dL is considered discretionary. Drug therapy in patients with LDL-C < 100 mg/dL is not provided as an option in the label. In 2001, when the current NCEP guidelines were released and subsequently incorporated by FDA into drug labeling, there was no convincing evidence for any benefit of lipid lowering drug therapy in patients with low to average LDL-C (i.e., LDL-C < 130 mg/dL).

However, the landmark Heart Protection Study provides clear evidence that patients with baseline LDL-C <100 mg/dL (n=3,421) benefit substantially from further lipid-lowering with simvastatin [redacted] If approved, these new uses of ZOCOR™ would be a significant improvement in the treatment of patients with either diabetes, a history of stroke or other cerebrovascular disease, peripheral vessel disease, or with existing CHD, to reduce mortality and cardiovascular morbidity.

Prior to HPS, there was no evidence from outcome studies to support treatment of diabetic patients without CHD to reduce cardiovascular morbidity. HPS included 5,963 diabetics of whom 3,982 had no CHD. Diabetics experienced treatment benefits with simvastatin therapy, with highly significant benefits seen separately in diabetic patients without CHD. Thus, the Heart Protection Study is the first to demonstrate that a drug therapy - simvastatin - reduces cardiovascular morbidity in diabetic patients without CHD.

Based on the beneficial effects of ZOCOR™ 40 mg on outcomes in patients: [redacted] From a public health perspective, there is an enormous need to implement the HPS findings. Based on data from NHANES III and the 2001 census, we estimate there are about 2 million patients with CHD with LDL-C below 100 mg/dL and about 8 million patients with diabetes but no CHD. Given the lack of approved therapies to reduce cardiovascular outcomes in these two populations, a significant unmet medical need exists. [redacted]

Furthermore, based on the evidence in HPS that liver function test (LFT) monitoring [redacted]

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in the *Labeling, Clinical, and Statistical* Sections of the approved New Drug Application for ZOCOR™. The Statement of Organization following this letter describes the sections contained in this application.

The study was conducted in the United Kingdom by the Clinical Trials Service Unit (CTSU) at the University of Oxford (Principal Investigator, Dr. Rory Collins), with financial support from the U.K. Medical Research Council, British Heart Foundation, Merck & Co., Inc. (who also supplied simvastatin), and Hoffman-LaRoche (who also supplied the antioxidant vitamin mixture).

A formal request for a full waiver from requirements of the December 2, 1998 Pediatric Final Rule (CFR 21.314.55(b)) is contained within Item 20 of this application. Please note that at the December 21, 2001 meeting it was agreed that pediatric studies will not be required for the proposed new use.

The Microsoft WORD version of the proposed labeling text is also supplied as PROPOSED.DOC within the labeling folder on the DLT tape provided.

This supplemental application is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs*. As an attachment to this letter, MRL is providing one DLT 20/40 Tape which contains the supplemental application which is approximately 7.5 GB. The DLT 20/40 Tape was created using Windows NT Backup utility software.

We have taken precautions to ensure that the content of this tape is free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorize the use of anti-virus software, as appropriate. All documents requiring signatures for certification are included as paper for archival purposes.

A list of reviewers from the Division of Metabolic and Endocrine Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Margaret Simoneau, R.Ph., M.S., Senior Regulatory Project Manager, Division of Metabolic and Endocrine Drug Products.

Reference is made to 21 CFR Part 54, *Financial Disclosure Investigators*. Data from one clinical study (Protocol 102) are presented in this application. Financial Disclosure certification and disclosure information as outlined in the regulations are provided under Item 19.

In accordance with the Prescription Drug User Fee Act of 1992 (PDUFA) and reauthorized in the Food and Drug Administration Modernization Act of 1997 (FDAMA), a check (Check No. C06094931), in the amount of $156,660.00, was sent to the Mellon Bank Services Center, Pittsburgh, PA on May 31, 2002. The User Fee I.D. number is / —/

Merck & Co., Inc. is requesting a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR 25.31(b). This supplement meets the requirements of a categorical exclusion under 21 CFR 25.31(b) because the estimated concentration of the drug substance at the point of entry, referred to as the Expected Introduction Concentration (EIC), into the aquatic environment is below 1 part per billion (ppb). While the patient use of simvastatin is at a level where the compound would theoretically exceed 1 ppb, conservatively, only 42% of parent compound or active metabolites remain in urine and feces. Thus the effective EIC for the parent compound and active metabolites is below 1 ppb. To the best of the firm's knowledge no extraordinary circumstances exist in regards to this action.

We consider the filing of this supplemental New Drug Application to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this supplemental application should be directed to Michael C. Elia, Ph.D., DABT (484-344-3180) or, in my absence, to Edwin L. Hemwall, Ph.D. (484-344-2306).

Sincerely,

M. C. Elia

Michael C. Elia, Ph.D., DABT
Senior Director, Regulatory Affairs

Enclosure: DLT 20/40 Tape

Hand Deliver

Desk Copies:

[redacted]R.Ph., M.S., Senior Regulatory Project Manager
(cover letter)
HFD-510, Room 14B-19
Parklawn Building
5600 Fishers Lane
Rockville, MD 20857
Federal Express #2

Dr. Robert J. Meyer, M.D., Director, ODE II
HFD-102, Room 13B-28
Parklawn Building
5600 Fishers Lane
Rockville, MD 20857
Federal Express #3

Maryann Holovac (cover letter and patent information)
Food and Drug Administration
HFD-090, Room 3012
12420 Parklawn Drive
Rockville, MD 20857
Federal Express #4

Q:\Nolt\NDA19-766\HPS\sNDA\HPS cover letter.doc

Simvastatin – Heart Protection Study
B. Proposed Text of Labeling

1. Annotated Package Circular

This section contains the annotated package circular. For those annotations that have two references, the first reference is to the "Executive Summary" subsection contained in Item 3 of this supplement. The page number indicates the location of a brief description of the information supporting the labeling statement. The second reference is to the specific technical sections contained in Item 8 of this supplement and gives the page numbers where a more detailed description of the supporting data can be found.

19-766/S-058
6/18/02 / 19 Stamp

# 49 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Administrative-* 14-~~766~~ SOSB

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004

# USER FEE COVER SHEET

***See Instructions on Reverse Side Before Completing This Form***

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Merck & Co., Inc.
Sumneytown Pike, BLA-10
P.O. Box 4
West Point, PA 19486

2. TELEPHONE NUMBER *(Include Area Code)*

( 484 ) 344-2383

3. PRODUCT NAME

ZOCOR™ (simvastatin)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N019766

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4333

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
*(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
*(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
*(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
*(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
*(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO
*(See item 8, reverse side if answered YES)*

**Public reporting burden for this collection of information** is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

Bonnie J

TITLE
Bonnie J. Goldmann, M.D.
Vice President, Regulatory Affairs

DATE
31 May 2002

FORM FDA 3397 (3/01)