

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-766/S-067, S-068

Trade Name: Zocor

Generic Name: simvastatin

Sponsor: Merck & Company

Approval Date: February 24, 2004

Indications: In addition to a diet restricted in saturated fat and cholesterol, reductions in risk CHD mortality and cardiovascular events; patients with hypercholesterolemia requiring modifications of lipid profiles; adolescent patients with heterozygous familial hypercholesterolemia.

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**APPLICATION NUMBER:
19-766/S-067, S-068**

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
19-766/S-067, S-068

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-766/S-067, S-068

Merck & Co., Inc.
Attention: Andrew M. Tershakovec, M.D.
Director, Regulatory Affairs
Sumneytown Pike, P.O.Box 4, BLA-20
West Point, PA 19486

Dear Dr. Tershakovec:

Please refer to your supplemental new drug applications, S-067, dated August 28, 2003, received August 29, 2003, and S-068, dated November 10, 2003, received November 12, 2003, submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for Zocor (simvastatin) Tablets.

We acknowledge receipt of your submission dated February 20, 2004.

Supplement-067 provides for revisions to the **PRECAUTIONS, Geriatric Use** subsection of the package insert.

To the **PRECAUTIONS, Geriatric Use** subsection, a new last sentence has been added to read:

There were no overall differences in safety between older and younger patients in either 4S or HPS.

Supplement-068 provides for revisions to the **DOSAGE AND ADMINISTRATION** section of the package insert.

To the **DOSAGE AND ADMINISTRATION** section, second paragraph, last sentence has been changed to read:

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, or gemfibrozil).

We completed our review of these applications, as amended. These applications are 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 February 20, 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 15 of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 19-766 /S-067, S-068." Approval of these submissions by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. 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, HFD-410
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
2/24/04 03:25:00 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
19-766/S-067, S-068

LABELING



MERCK & CO., INC.

Whitehouse Station, NJ 08889, USA

955664495566XX

TABLETS

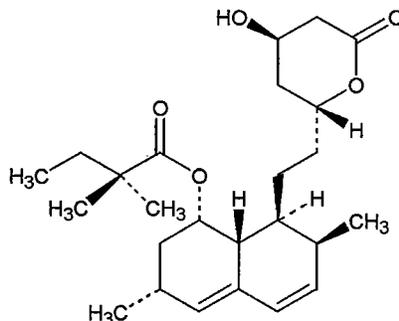
ZOCOR®

(SIMVASTATIN)

DESCRIPTION

ZOCOR¹ (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-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1 α ,3 α ,7 β ,8 β (2S*,4S*),-8a β]]. The empirical formula of simvastatin is C₂₅H₃₈O₅ 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.
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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 study², 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 first² 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 (25th and 75th 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 Lijja 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 method³ 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 (5%) 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

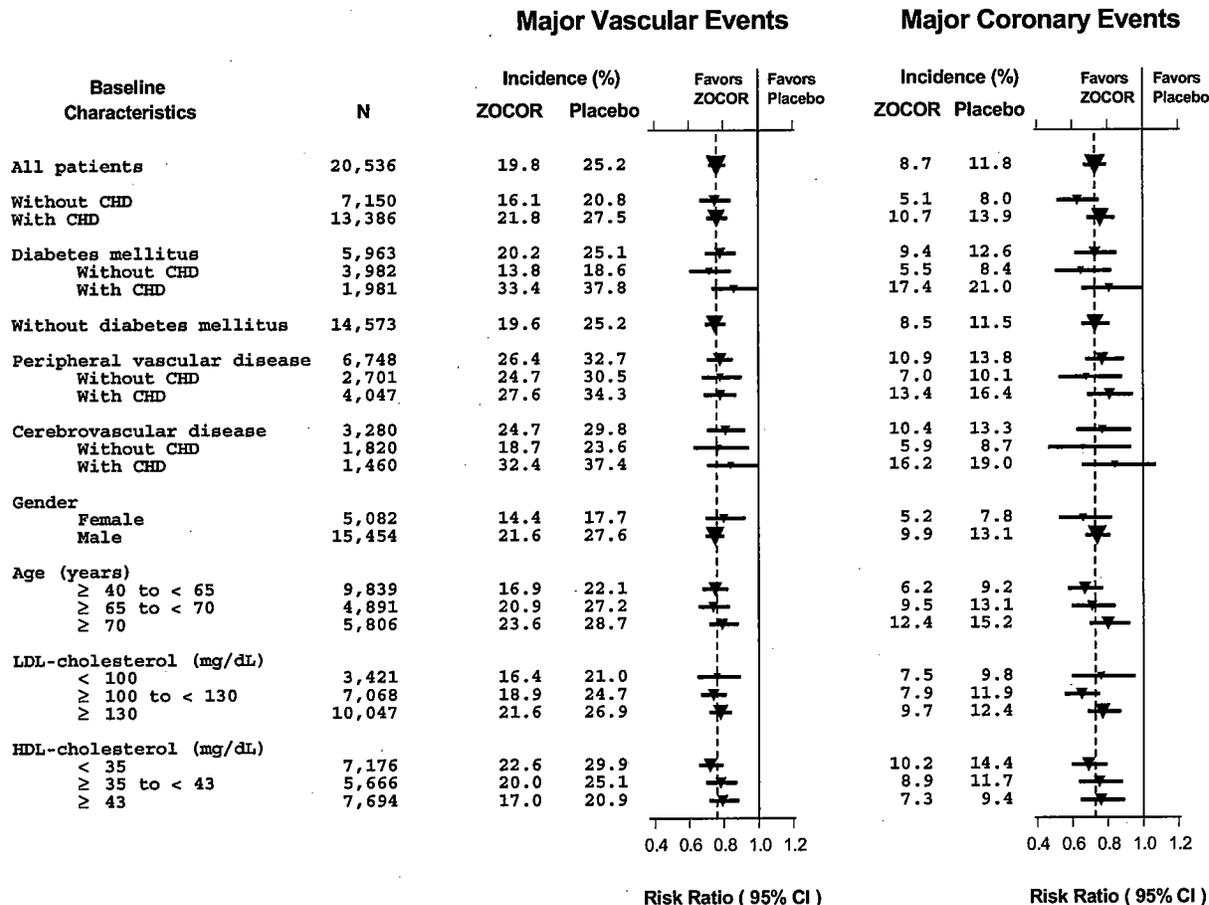
| Endpoint | ZOCOR (N=10,269) n (%)† | Placebo (N=10,267) n (%)† | Risk Reduction (%) (95% CI) | p-Value |
|---|-------------------------------|---------------------------------|--------------------------------|----------|
| Primary | | | | |
| Mortality | 1,328 (12.9) | 1,507 (14.7) | 13 (6-19) | p=0.0003 |
| 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.

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

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



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 [†] |
|--|------|---------|-------|-------|-----------------|
| <u>Lower Dose Comparative Study</u> (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 |
| <u>Scandinavian Simvastatin Survival Study</u> (Mean % Change at Week 6) | | | | | |
| Placebo | 2223 | -1 | -1 | 0 | -2 |
| ZOCOR 20 mg q.p.m. | 2221 | -28 | -38 | 8 | -19 |
| <u>Upper Dose Comparative Study</u> (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 |
| <u>Multi-Center Combined Hyperlipidemia Study</u> (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 premenopausal 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 IIb⁴).
- 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 $\leq 20\%$) | < 130 | ≥ 130 | 10-year risk 10-20%: ≥ 130 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*).

Other drugs:

Gemfibrozil particularly with higher doses of simvastatin (see below; PRECAUTIONS, *Drug Interactions*, *Interactions with lipid-lowering drugs that can cause myopathy when given alone*; DOSAGE AND ADMINISTRATION).

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

Amiodarone or verapamil with higher doses of simvastatin (see below; 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 gemfibrozil. The combined use of simvastatin with gemfibrozil should be avoided, unless the benefits are likely to outweigh the increased risks of this drug combination. Caution should be used when prescribing other lipid-lowering drugs (other fibrates or lipid-lowering doses (≥ 1 g/day) of niacin) with simvastatin, as these agents can cause myopathy when given alone. **The benefit of further alterations in lipid levels by the combined use of simvastatin with fibrates or niacin should be carefully weighed against the potential risks of these combinations.** Addition of fibrates or niacin 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 10 mg daily in patients receiving concomitant medication with cyclosporine. The benefits of the use of simvastatin in patients receiving cyclosporine should be carefully weighed against the risks of this combination.

4. 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.

5. 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.

6. 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

See WARNINGS, *Myopathy/Rhabdomyolysis*.

The risk of myopathy is increased by gemfibrozil (see **DOSAGE AND ADMINISTRATION**) and to a lesser extent by other fibrates and 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 ensure 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/m²), 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/m² 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 review⁵ 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

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.

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.

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. 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. There were no overall differences in safety between older and younger patients in either 4S or HPS.

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) % |
|--|---------------------------|---------------------------|----------------------------------|
| <i>Body as a Whole</i> | | | |
| Abdominal pain | 3.2 | 3.2 | 8.9 |
| Asthenia | 1.6 | 2.5 | 1.1 |
| <i>Gastrointestinal</i> | | | |
| Constipation | 2.3 | 1.3 | 29.1 |
| Diarrhea | 1.9 | 2.5 | 7.8 |
| Dyspepsia | 1.1 | — | 4.5 |
| Fatulence | 1.9 | 1.3 | 14.5 |
| Nausea | 1.3 | 1.9 | 10.1 |
| <i>Nervous System/ Psychiatric</i> | | | |
| Headache | 3.5 | 5.1 | 4.5 |
| <i>Respiratory</i> | | | |
| 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 $\geq 0.5\%$ 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) % |
|-------------------------|---------------------------|-----------------------------|
| <i>Body as a Whole</i> | | |
| Abdominal pain | 0.9 | 0.9 |
| <i>Gastrointestinal</i> | | |
| Diarrhea | 0.5 | 0.3 |
| Dyspepsia | 0.6 | 0.5 |
| Flatulence | 0.9 | 0.7 |
| Nausea | 0.4 | 0.6 |
| <i>Musculoskeletal</i> | | |
| Myalgia | 1.2 | 1.3 |
| <i>Skin</i> | | |
| Eczema | 0.8 | 0.8 |
| Pruritus | 0.5 | 0.4 |
| Rash | 0.6 | 0.6 |
| <i>Special Senses</i> | | |
| 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 erythematosus-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 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/m². No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 g/m², 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; the maximum dose taken was 3.6 g. All patients recovered without sequelae. 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, or gemfibrozil).

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 Guidelines⁶ 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, 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*).

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

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.

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,
Cramlington, Northumberland, UK NE23 3JU

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ZOCOR® (simvastatin)

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
19-766/S-067, S-068

MEDICAL REVIEW

MEDICAL OFFICER REVIEW

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

| | |
|-----------------------------------|-------------------------------|
| Application #:19766 SLR 067 | Application Type:NDA |
| Sponsor:Merck Research Labs | Proprietary Name:Zocor |
| Investigator:Multiple (Not named) | USAN Name:simvastatin |
| Category:Lipid-lowering agent | Route of Administration: Oral |
| Reviewer:William Lubas MD-PhD | Review Date:2/11/04 |

SUBMISSIONS REVIEWED IN THIS DOCUMENT

| Document Date | CDER Stamp Date | Submission Type | Comments |
|---------------|-----------------|-------------------------------|--|
| Aug. 28, 2003 | Sept. 2, 2003 | SLR Labeling supplement | Reanalysis of HPS data to update <i>Geriatric Use</i> section of the Zocor label |

RELATED APPLICATIONS (If applicable)

| Document Date | Application Type | Comments |
|---------------|------------------|---|
| June 18, 2002 | NDA's 058 | Original analysis of HPS approved April 16, 2003 |

REVIEW SUMMARY:

As part of the labeling negotiations for the Heart Protection Study (HPS), the sponsor agreed to a reanalysis of the safety data to obtain geriatric safety information that could be used to update the product labeling. The Oxford analysis of the data found only one category that was statistically more frequent in elderly patients (≥ 65) on simvastatin compared to placebo i.e. "thyroid or parathyroid disease or surgery". An analysis of the serious adverse events (REPTTERMs) that make up this category showed that this finding was primarily driven by an increase in the number of cases of "hypothyroidism/myxedema" (13 vs. 5). It is not clear why "hypothyroidism/myxedema" should be more common in patients in the simvastatin group compared to placebo. Given the large numbers of comparisons ($n=104$) made in this analysis, without adjustment for multiplicity, it is likely that at least one of these would be a chance occurrence. In contrast, there were multiple adverse events that were more common in elderly patients (≥ 65) on placebo compared to simvastatin, which likely are related to the cardiovascular benefits from statin use.

Because of the trial design all patients were exposed to simvastatin for a 6 week run-in period prior to randomization. It is possible therefore, that more susceptible patients may have been culled from the trial because of adverse events, which may or may not have been reported, during this period. For example there were two patients who had rhabdomyolysis during the 6 week run-in period that were not included in the study and are not part of this final analysis. Therefore, these data may underestimate the true frequency of adverse events, but there is no reason to suspect that the run-in period would have affected the age distribution of the observed adverse events.

In conclusion, there is no evidence in this data set of an overall increase in serious adverse events in elderly patients (≥ 65) in the simvastatin group compared to placebo.

RECOMMENDED REGULATORY ACTION:

| | | |
|----------------------------|---------------------|-------------------------|
| New clinical studies _____ | Clinical Hold _____ | Study May Proceed _____ |
| NDA, Efficacy/Label _____ | X Approvable _____ | Not Approvable _____ |

supplement:

CLINICAL REVIEW

Clinical Review Section

| | |
|--|------------------------|
| SIGNATURES: Medical Reviewer: <u>William Lubas MD-PhD</u> | Date: 2/11/2004 |
| Medical Team Leader: <u>Mary Parks MD</u> | Date: 2/11/2004 |

CLINICAL REVIEW

Clinical Review Section

Introduction:

The Heart Protection Study (HPS) was a large multicenter, 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. The original supplement was reviewed and approved on April 16, 2003. As part of the labeling negotiations the sponsor agreed to reanalyze the safety data to obtain information that could be used to update the *Geriatrics Use* section of the Zocor label and this information has been included in this submission.

The Oxford investigators performed a post hoc subgroup analysis of serious adverse events in patients according to age, i.e. <65 (simvastatin n=4903, placebo n=4936) and ≥65 (simvastatin n=5366, placebo n=5331). These data were subgrouped using the following categories:

Cerebrovascular events

- subdural hematoma
- carotid stenosis
- possible TIAs (simvastatin statistically better in patients ≥65)
- retinal artery occlusion (simvastatin statistically better in patients <65)

Other Cardiovascular

- cardiovascular symptom or investigation
- coronary angiography
- other or unspecified angiography
- hypertension
- heart failure (simvastatin statistically better in patients <65)
- arrhythmia, conduction disorder, pacemaker
- endocarditis, pericarditis, pericardial surgery
- other heart surgery or procedure
- other PVD admissions (simvastatin statistically better in patients ≥65)
- other vascular surgery or procedure
- DVT
- phlebitis, varicose vein surgery, vein occlusion
- pulmonary embolus
- other cardiovascular disease (simvastatin statistically better in patients <65)

Accidents/trauma

- falls
- fracture of any kind
- fracture of hip, wrist, or spine
- other fracture
- soft tissue or other injury (simvastatin statistically better in patients <65)
- road traffic accident
- overdose or suicide attempt
- any accidents or trauma

CLINICAL REVIEW

Clinical Review Section

Blood disorders

anemia or blood loss (simvastatin statistically better in patients <65)
clotting disorders
blood cell disorders

Endocrine

unstable diabetes or complications
diabetic foot ulcer
laser treatment for retinopathy
thyroid or parathyroid disorder or surgery (simvastatin statistically worse in patients ≥65)
breast disease
other endocrine problem

ENT disease

epistaxis
other ENT symptoms
ear condition or surgery
nose and sinus surgery
laryngeal surgery and bronchoscopy
mouth or throat surgery

Eye disease

retinal problem
eye infection, inflammation, visual symptoms or problem
eye vascular problem
glaucoma or glaucoma surgery
cataract or cataract removal
other eye surgery

Gastrointestinal (GI)

gastrointestinal symptoms or investigation
esophageal disease or surgery
peptic ulcer disease or surgery, gastritis, stomach problem
gall bladder disease or surgery
liver disease
pancreatic disease or surgery
appendix disease or appendectomy
hernia
other GI disease including colitis
bowel and other GI surgery (simvastatin statistically better in patients ≥65)
endoscopy or barium investigation
gastroenteritis

CLINICAL REVIEW

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Genitourinary (GU)

- GU symptoms or investigation
- renal failure
- urinary tract problem including infection and stones
- prostate problem (simvastatin statistically worse in patients <65)
- bladder problem
- kidney surgery
- testicular or other genitourinary problem
- gynecological surgery or problems
- any genito-urinary disease

Musculoskeletal

- myopathy or rhabdomyolysis
- other muscle problems
- bone disease
- arthritis
- spondylitis, spondylosis, back pain or sciatica
- any joint injury
- hip surgery
- soft tissue surgery or disease

Neurological

- neurological symptoms or investigation
- chronic neurological disease
- sleep problem
- peripheral nerve surgery, neuropathy, or spinal cord problem
- other neurological disease or procedure

Psychological

- dementia
- confusion, psychosis, schizophrenia
- depression or bladder disease
- any psychological problem or symptoms

Respiratory

- respiratory symptoms or investigations
- acute respiratory infections including sinus problems
- pneumonia and influenza
- COPD or asthma
- other respiratory disease (simvastatin statistically better in patients <65)
- chest wall surgery or procedure
- any respiratory

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Skin

rash, urticaria, various skin conditions
 skin infection (simvastatin statistically better in patients <65)
 skin change
 leg ulcers
 skin surgery

Other

general or non-specific symptoms (simvastatin statistically better in patients ≥65)
 other investigations, biopsies and assessments
 chemotherapy or radiotherapy
 septicemia (simvastatin statistically better in patients ≥65)
 other infections including viruses
 post-operative complications (simvastatin statistically better in patients ≥65)
 adverse drug reaction or allergies

“SIMVASTATIN IS WORSE”-

Treatment with simvastatin resulted in more statistically significant serious adverse events compared to placebo in only two AE (adverse event) categories (see Table 1). “Thyroid or parathyroid disease or surgery” was more common in patients ≥65 years of age and “prostate problems” was more common in patients under 65 years of age.

| Table 1 | | | | |
|--|---|---------------------------|-----------------------|----------------------|
| REPTTERM categories with statistically significant differences between simvastatin and placebo groups in which “Simvastatin is Worse” | | | | |
| Age | AE category | Pts on Simvastatin | Pts on Placebo | Relative Risk |
| 65 and over | thyroid or parathyroid disease or surgery | 21 (0.4%) | 9 (0.2%) | 2.2 |
| Under 65 | Prostate problem | 103 (2.1%) | 75 (1.5%) | 1.4 |
| Data from Oxford analysis, Appendix 1 in submission | | | | |

Using the computer program Jump to identify the serious adverse events (REPTTERMs) associated with “thyroid and parathyroid disease”, it is possible to identify 69 different patients with serious adverse events (3 patients were listed in two different (REPTTERM) categories).

CLINICAL REVIEW

Clinical Review Section

| Table 2 Serious adverse events in patients with thyroid and parathyroid disease categorized by age (≥ 65 or < 65) and treatment group (Simva vs Placebo) | | | | |
|---|--|--------------|---------------------------------|----------------|
| Age | REPTTERM | Simva | REPTTERM | Placebo |
| 65 and Older | adverse reactions to thyroxine/ thyroid-derived products | 1 | | |
| | hyperthyroidism/ thyrotoxicosis | 5 | hyperthyroidism/ thyrotoxicosis | 3 |
| | hypothyroidism/ myxoedema | 13 | hypothyroidism/ myxoedema | 5 |
| | parathyroid adenoma | 1 | | |
| | parathyroidectomy | 1 | | |
| | thyroid cancer/ cancer thyroid | 1 | | |
| | thyroid problems | 2 | thyroid problems | 2 |
| | | | | |
| Under 65 | adverse reactions to thyroxine/ thyroid-derived products | 1 | | |
| | hyperthyroidism/ thyrotoxicosis | 2 | hyperthyroidism/ thyrotoxicosis | 3 |
| | hypothyroidism/ myxoedema | 11 | hypothyroidism/ myxoedema | 6 |
| | thyroid cancer/ cancer thyroid | 1 | | |
| | | | thyroid cyst or benign nodule | 1 |
| | thyroid operations | 1 | | |
| | thyroid problems | 1 | thyroid problems | 2 |
| | thyroidectomy | 5 | thyroidectomy | 4 |

The greatest difference between treatment groups was seen in the category of hypothyroidism/myxedema with consistently more patients in the simvastatin versus placebo groups for both patients 65 and older ($13/5=2.6$) and for patients under 65 years of age ($11/6=1.8$). It is not clear why hypothyroidism is associated with use of simvastatin in this study. Given the large numbers of comparisons made in this analysis, without adjustment for multiplicity ($n=104$), it is likely that this may be a chance occurrence. Of note, hypothyroidism is not mentioned as a common adverse event in the Zocor label.

A similar analysis was performed on the serious adverse events (REPTTERMs) associated with "prostate problem". This showed more cases of "prostate operation unspecified/prostatectomy unspecified" (48 vs. 31), "prostate cancer/cancer of the prostate" (29 vs. 21) and "biopsy of the prostate" (10 vs. 3) in patients under 65 years of age in the simvastatin group compared to the placebo group. Given the large numbers of comparisons made in this analysis, without adjustment for multiplicity, it is likely that these too may be chance occurrences. Of note, prostate disease is not mentioned as a common adverse event in the Zocor label.

"SIMVASTATIN IS BETTER"-

In contrast, to only two adverse event categories which were more common in patients taking simvastatin, there were multiple adverse event categories in which the simvastatin group had fewer events than placebo. These serious AE categories are listed in Table 3.

CLINICAL REVIEW

Clinical Review Section

Table 3
REPTTERM categories with statistically significant differences between simvastatin and placebo groups in which "Simvastatin is Better"

| Age | AE category | Pts on Simvastatin | Pts on Placebo | Relative Risk |
|--------------------|------------------------------|--------------------|----------------|---------------|
| 65 and over | Possible TIAs | 162 (3.0%) | 202 (3.8%) | 0.78 |
| | Other PVD admissions | 44 (0.8%) | 64 (1.2%) | 0.68 |
| | Bowel and other GI surgery | 294 (5.5%) | 351 (6.6%) | 0.82 |
| | General or nonspecific Sxs | 145 (2.7%) | 187 (3.5%) | 0.76 |
| | Septicemia | 14 (0.3%) | 32 (0.6%) | 0.45 |
| | Post-operative complications | 54 (1.0%) | 87 (1.6%) | 0.61 |
| | | | | |
| Under 65 | Retinal artery occlusion | 1 (0.0%) | 7 (0.1%) | 0.22 |
| | Heart failure | 83 (1.7%) | 117 (2.4%) | 0.71 |
| | Other CV disease | 9 (0.2%) | 23 (0.5%) | 0.42 |
| | Soft tissue injury | 34 (0.7%) | 54 (1.1%) | 0.63 |
| | Anemia or blood loss | 27 (0.6%) | 45 (0.9%) | 0.61 |
| | Other respiratory Dz | 10 (0.2%) | 24 (0.5%) | 0.44 |
| | Skin infection | 51 (1.0%) | 75 (1.5%) | 0.68 |
| | | | | |

Data from Sponsor's submission Appendix 1

Many of these differences are probably related to the cardiovascular benefits associated with statin use, although given the large number of comparisons made, without adjustment for multiplicity, some of these may be chance occurrences, as well.

DATA ANALYSIS USING JUMP-

Oxford analyzed the data by subdividing it into 104 different related categories. Each category was made up of a combination of different serious adverse event (REPTTERM) subgroups. Since the number of serious adverse events in only two of these categories was statistically significantly greater in patients in the simvastatin group versus the placebo group, I performed my own analysis of the individual serious adverse events (REPTTERMs) to see if there might be additional individual adverse events (REPTTERMs) that have a statistically significant greater number of patients in the simvastatin group versus placebo. The results of this analysis are shown in Table 4.

Serious adverse events were supplied electronically at \\Cdsesub1\N19766\S_058\2002-06-18\crt\datasets\102, file AE.xpt in the original NDA submission. Adverse events were grouped by PREFTERM (general) and REPTTERM (specific) and a unique patient identifier, PTID. Each item with a single PTID and REPTTERM was counted as a single event. So each patient with a specific adverse event was counted only once. Adverse events were grouped by age i.e. ≥ 65 or < 65 years of age and treatment group i.e. simvastatin (+/- vitamins) or placebo (+/-vitamins).

CLINICAL REVIEW

Clinical Review Section

Table 4
Adverse events (REPTTERMs) which occurred more frequently in patients on simvastatin compared to placebo

| Age (yr) | REPTTERM | Simvastatin | Placebo | p-value | |
|---------------|---|----------------|----------------|---------------|-------------------|
| | | Patient number | Patient number | Binomial Test | Fisher Exact Test |
| ≥65 | | N=5366 | N=5331 | | |
| | awaiting investigation/under investigation | 5 | 0 | 0.026 | 0.032 |
| | fracture collar bone/ clavicle fracture | 5 | 0 | 0.026 | 0.032 |
| | hydrocoele | 5 | 0 | 0.026 | 0.032 |
| | brain tumour/ brain cancer | 10 | 2 | 0.021 | 0.020 |
| | solar keratosis | 15 | 4 | 0.012 | 0.010 |
| | hypothyroidis/myxedema | 13 | 5 | 0.061 | 0.049 |
| | bladder operations | 17 | 5 | 0.011 | 0.009 |
| | eye operation unspecified | 25 | 11 | 0.020 | 0.015 |
| | cataract | 28 | 15 | 0.049 | 0.034 |
| | scc/squamous cell ca | 37 | 17 | 0.007 | 0.005 |
| <65 | | N=4903 | N=4936 | | |
| | ace inhibitor trial | 5 | 0 | 0.025 | 0.031 |
| | colitis unspecified | 5 | 0 | 0.025 | 0.031 |
| | ct scan | 5 | 0 | 0.025 | 0.031 |
| | renal artery angioplasty | 5 | 0 | 0.025 | 0.031 |
| | vaginal bleeding/ pv bleed | 5 | 0 | 0.025 | 0.031 |
| | laminectomy | 7 | 0 | 0.008 | 0.008 |
| | biopsy of the prostate | 10 | 3 | 0.051 | 0.045 |
| | hematemesis | 13 | 3 | 0.012 | 0.010 |
| | prostate operation unspecified/prostatectomy unspecified | 48 | 31 | 0.051 | 0.033 |

The 2-sided binomial test, p-value was calculated using a normal approximation to the binomial without a continuity correction. No adjustment was made for multiplicity. <http://cdernet/dtd/HANDOUTS/Spring2000/bascstat/bslec7.xls>
 The Fisher Exact test was performed using the online test from St. John's Univ. at: <http://www.physics.csbsju.edu/stats/fisher.form.html>

A total of 1177 different serious adverse events (REPTTERMs) were analyzed so it is possible that most of the small number of positives seen here may have occurred by chance. The only AE category with more adverse events in patients receiving simvastatin compared to placebo identified by the Oxford group in patients over 65 years of age was “thyroid and parathyroid disease or surgery”. This finding is consistent with the serious adverse event (REPTTERM) “hypothyroidism/myxedema” seen in Table 4, which is barely statistically significant i.e. 13 vs. 5, p=0.061 (binomial test) p=0.049 (Fisher Exact test). The only AE category with more adverse events in patients receiving simvastatin compared to placebo identified by the Oxford groups in patients under 65 years of age was “prostate problems”. This finding is consistent with the serious adverse event (REPTTERM) categories of “biopsy of the prostate” and “prostate biopsy and prostate operation” shown to be statistically significant in Table 4. The category “eye operations unspecified” and “cataracts” may also be related to statin use. The current Zocor label

CLINICAL REVIEW

Clinical Review Section

already mentions the potential for progression of cataracts. However, most of these adverse event (REPTTERM) categories seen in Table 4 can not clearly be associated with previously identified statin-related adverse events and are likely to be chance occurrences.

MYOPATHY-

The incidence of myopathy or rhabdomyolysis was low in this 5 year study (<0.1%). The Oxford analysis showed that there were more patients with “myopathy or rhabdomyolysis” on simvastatin versus placebo in both patients under 65 years of age (3 vs. 1) and in patients 65 years of age and over (6 vs. 3). However, the number of cases was too small to show statistical significance, and there was no trend suggesting a higher frequency in the elderly patients taking simvastatin compared to placebo as had occasionally been seen in other studies with statins. These data, however, may underestimate the true frequency of myopathy in patients treated with simvastatin because the study design exposed all patients to simvastatin during a 6 week run-in period. Patients who might be more susceptible to muscle symptoms may have been culled from the population prior to randomization. In fact, there were two patients who had rhabdomyolysis during the 6 week run-in period that were not included in the study and are not part of this final analysis.

LIVER-RELATED ADVERSE EVENTS-

The Oxford analysis found no difference in the frequency of liver disease in patients on simvastatin versus placebo for patients <65 [16 (0.3%) vs. 17 (0.3%)] or ≥ 65 [13 (0.2%) vs. 14 (0.3%)]. The number of individual liver-related serious adverse events (REPTTERM) was too small to show statistical significance and there was no trend suggesting a higher frequency in the elderly patients. These data, however, may underestimate the true frequency of liver disease in patients treated with simvastatin because the study design exposed all patients to simvastatin during a 6 week run-in period. Patients who might be more susceptible to liver symptoms may have been culled from the population prior to randomization.

PROPOSED LABELLING CHANGES-

The sponsor proposes deleting the line

“There were no overall differences in safety between older and younger patients in 4S.”

from the middle of the *Geriatric Use* section and adding the following line to the end of the current *Geriatric Use* section:

“There were no overall differences in safety between older and younger patients in either 4S ~~or HPS~~”.

SUMMARY-

The sponsor’s proposed labeling changes are consistent with this medical officer’s review of the data in this present submission.

RECOMMENDATION

Approve proposed labeling change.

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/s/

William Lubas
2/23/04 12:41:39 PM
MEDICAL OFFICER

Mary Parks
2/23/04 03:51:52 PM
MEDICAL OFFICER

Medical Officer's Review of Labeling Supplement/CBE

NDA#: 19-766; S068 (CBE)
Drug: Zocor (simvastatin)
Sponsor: Merck & Co., Inc.
Reviewer: Anne Pariser, M.D.
Date of Submission: 10-November-2003
Review Date: 20-November-2003

Re: Changes Being Effective (CBE) to correct error/omission noted in S065 Labeling Supplement (Regarding Concomitant Use of Fibrates with Simvastatin)

I. Introduction and Background

The sponsor (Merck & Co., Inc.) submitted a labeling supplement for Zocor (simvastatin): NDA 19-766; SLR 065, dated 18-March-2003, for labeling changes for the concomitant administration of fibrates and niacin with Zocor. Supplement 065 was approved 17-September-2003. After approval, it was noted by the Sponsor that there was an incorrect cross-reference in the Dosage and Administration section of the label, where reference is made to the subsection for "fibrates and niacin" instead of "gemfibrozil". The proposed CBE submission (NDA 19-766; S068, dated 10-November-2003) is to correct this cross-reference.

Supplement 065 has been previously reviewed and the findings of that review will not be reiterated here. Please see: Pariser A, M.D., Medical Officer's Review of Labeling Supplement NDA #19-766; S065, dated 03-September-2003, for complete details.

II. Review of Labeling Supplement Request

The specific, proposed change to the current label for Zocor appears in the Dosage and Administration section, second paragraph [the proposed changes appear as ~~strike-through~~ (deletion), and underline (addition)], as follows:

"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~~ gemfibrozil)."

The above change reflects changes made to the label per Supplement 065, specifically, the Dosage and Administration recommendations for patients taking Concomitant Lipid-Lowering Therapy, which are as follows [from Dosage and Administration section]:

“Concomitant Lipid-Lowering Therapy

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

No other changes were proposed (other than date changes to reflect last approved labeling and circular number).

III. Conclusion and Recommendation

The proposed change to the label in this CBE is consistent with the previous changes made to the label in Supplement 065. This Reviewer has no objections to the proposed labeling change.

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/s/

Anne Pariser
11/24/03 08:43:58 AM
MEDICAL OFFICER

Mary Parks
11/24/03 09:42:09 AM
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
19-766/S-067, S-068

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Division of Metabolic & Endocrine Drug Products

Labeling Review

Application Number: 19-766/S-067, S-068

Name of Drug: Zocor (simvastatin) Tablets

Sponsor: Merck

Submission Date: February 10, 2004 (e-mail) and February 20, 2004 submission

Background and Summary:

Zocor is indicated:

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.

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 supplements, S-065, S-066, were approved on September 17, 2003, (Package Identifier 9556644). Supplement-065 provided for revisions to the **WARNINGS, Myopathy/Rhabdomyolysis** subsection, **PRECAUTIONS, Interactions with lipid-lowering drugs that can cause myopathy when given alone** subsection, **ADVERSE REACTIONS, Concomitant Lipid Lowering Therapy** subsection, **OVERDOSAGE** section, and **DOSAGE AND ADMINISTRATION, Concomitant Lipid-Lowering Therapy** subsections of the package insert.

Supplement-066, a Changes Being Effected (CBE) supplement, provided for a correction of the computational error in the **CLINICAL PHARMACOLOGY, Reductions in Risk of CHD Mortality and Cardiovascular Events** subsection of labeling in supplement S-058.

Supplement-067 provides for revisions to the **PRECAUTIONS, Geriatric Use** subsection of the package insert.

Supplement-068 provides to correct the cross-reference in the **DOSAGE AND ADMINISTRATION** section of the package insert.

Reference is made to the post labeling review note from S-065, S-066 which read:

19-766/S-065, S-066 labeling supplement letter was signed on September 17, 2003. The Agency received a phone call from Merck on September 22, 2003, requesting that a labeling change be considered an annual reportable item. Under the **DOSAGE AND ADMINISTRATION** section, second paragraph, last sentence, request was for this sentence to read, "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, or gemfibrozil)." The accepted language reads: "...or for patients receiving concomitant therapy (i.e., cyclosporine, amiodarone, verapamil, fibrates or niacin)."

Drs. Pariser and Parks were consulted and it was determined that this requested change was a *Change Being Effected* (CBE) labeling supplement which needs to be submitted to the Agency. In a T-con on September 22, 2003, with Enid Galliers and Margaret Simoneau, Dr. Tershakovec of Merck was notified of this recommendation.

Review:

To the **PRECAUTIONS, Geriatric Use** subsection, a new last sentence (from the same paragraph with "or HPS" included) has been added to read:

There were no overall differences in safety between older and younger patients in either 4S or HPS.

To the **DOSAGE AND ADMINISTRATION** section, second paragraph, last sentence (from "fibrates or niacin" to "gemfibrozil") has been changed to read:

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, or gemfibrozil).

Conclusion:

The proposed draft label (Package Identifier Number 9556646), submitted February 20, 2004, was found acceptable by the reviewing team. The labeling review is from the MS Word version of the electronic draft labeling for S-065, S-066, package insert submitted September 12, 2003, approved on September 17, 2003. The Agency will issue an approval action on this supplement.

Reviewed by: M.A. Simoneau, R.Ph., Regulatory Project Manager
(See appended electronic signature page)

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/s/

Margaret Simoneau
2/26/04 02:53:41 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-766/S-067

PRIOR APPROVAL SUPPLEMENT

Merck & Company, Inc.
Attn: Andrew M. Tershakovec, M.D.
Director, Regulatory Affairs
Sumneytown Pike, P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Tershakovec:

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-067
Date of supplement: August 28, 2003
Date of receipt: August 29, 2003

This supplemental application provides for revisions to The *Geriatric Use* subsection of the package insert.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 28, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the goal date will be February 29, 2004.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA 19-766/S-067

Page 2

If you have any question, call me at (301) 827-6411.

Sincerely,

{See appended electronic signature page}

Margaret Simoneau, M.S., R.Ph.
Regulatory Project Manager
Division of Metabolic & Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Margaret Simoneau
9/5/03 09:11:02 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-766/S-068

CBE-0 SUPPLEMENT

Merck & Company, Inc.
Attn: Andrew M. Tershakovec, M.D.
Director, Regulatory Affairs
Sumneytown Pike, P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Tershakovec:

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-068

Date of supplement: November 10, 2003

Date of receipt: November 12, 2003

This supplemental application, submitted as "Supplement - Changes Being Effected," proposes to correct the cross-reference in the DOSAGE AND ADMINISTRATION section of the package insert for Zocor™.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 11, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 12, 2004.

NDA 19-766/S-068

Page 2

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Metabolic & Endocrine Drug Products, HFD-510

Attention: Fishers Document Room, 8B45

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, M.S., R.Ph.

Regulatory Project Manager

Division of Metabolic & Endocrine Drug Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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/s/

Margaret Simoneau
11/21/03 11:13:01 AM