

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 19-766/S045

Trade Name: Zocor Tablets

Generic Name: simvastatin

Sponsor: Merck & Company, Inc.

Approval Date: September 25, 2001

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APPLICATION NUMBER:
NDA 19-766/S045

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APPLICATION NUMBER:
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APPROVAL LETTER



NDA 19-766/S-045

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

Dear Dr. Elia:

Please refer to your supplemental new drug application dated November 7, 2000, received November 8, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zocor (simvastatin) tablets.

We note that this application was submitted as a change being effected (CBE) supplement. Upon review of this supplement it was determined that the proposed labeling changes require approval prior to their implementation. Accordingly, this application has been classified as a prior approval (PA) labeling supplement. Any changes to the current package insert that are based on this application will need to be withdrawn.

We have completed the review of this application, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit draft labeling revised as follows:

Under **WARNINGS; Skeletal Muscle**, change the proposed language to:

“The risk of myopathy appears to be increased by concomitant administration of verapamil (see PRECAUTIONS, Drug Interactions). 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 patients/21,224, 0.061%).”

Under **PRECAUTIONS**, change the proposed language to:

“The risk of myopathy appears to be increased by concomitant administration of verapamil.”

Under **ADVERSE REACTIONS**:

The proposal to include “dermatomyositis” in the label is acceptable

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with the proposed changes prior to approval of this supplemental application.

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

**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
9/25/01 09:29:48 PM

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APPLICATION NUMBER:
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LABELING



MERCK & CO., INC.

Whitehouse Station, NJ 08889, USA

782544X

TABLETS

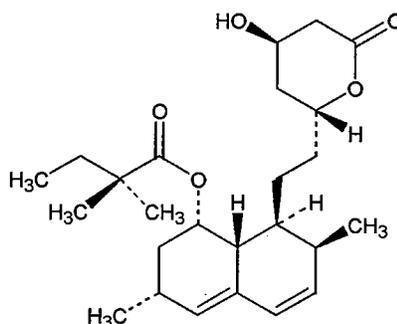
ZOCOR®

(SIMVASTATIN)

DESCRIPTION

ZOCOR* (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)

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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 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.

Simvastatin is a substrate for CYP3A4 (see PRECAUTIONS, *Drug Interactions*). Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma concentrations of drugs metabolized by CYP3A4. In one study**, 10 subjects consumed 200 mL of double-strength grapefruit juice (one can of frozen concentrate diluted with one rather than 3 cans of water) three times daily for 2 days and an additional 200 mL double-strength grapefruit juice together with and 30 and 90 minutes following a single dose of 60 mg simvastatin on the third day. This regimen of grapefruit juice resulted in mean increases in the concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [measured using a radioenzyme inhibition assay both before (for active inhibitors) and after (for total inhibitors) base hydrolysis] of 2.4-fold and 3.6-fold, respectively, and of simvastatin and its β -hydroxyacid metabolite [measured using a chemical assay — liquid chromatography/tandem mass spectrometry] of 16-fold and 7-fold, respectively. In a second study, 16 subjects consumed one 8 oz glass of single-strength grapefruit juice (one can of frozen concentrate diluted with 3 cans of water) with breakfast for 3 consecutive days and a single dose of 20 mg simvastatin in the evening of the third day. This regimen of grapefruit juice resulted in a mean increase in the plasma concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [using a validated enzyme inhibition assay different from that used in the first** 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.

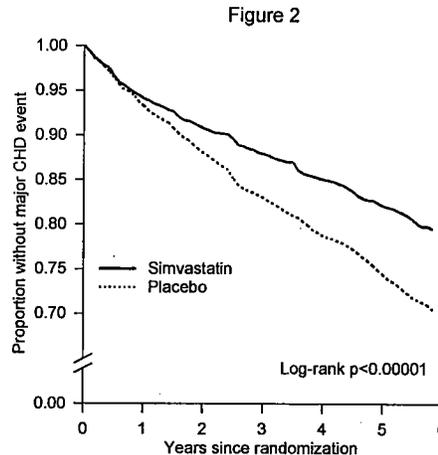
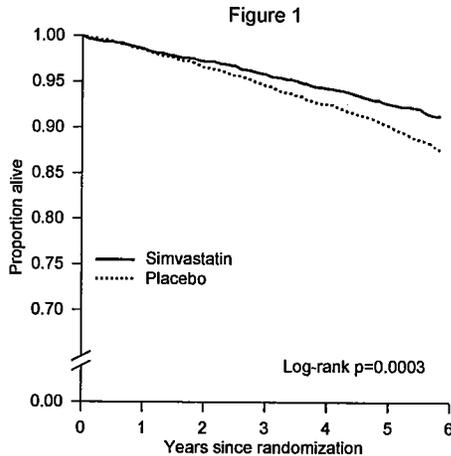
Clinical Studies

Coronary Heart Disease

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 (Figure 1) 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]) (Figure 2) 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.

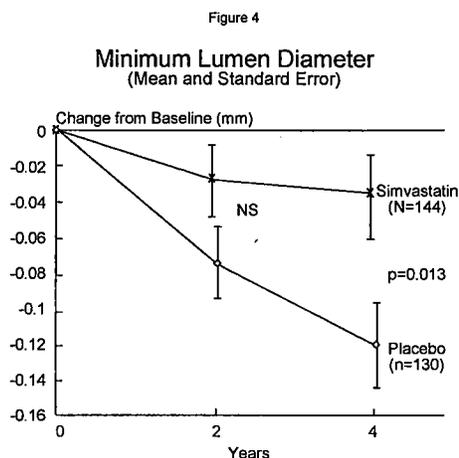
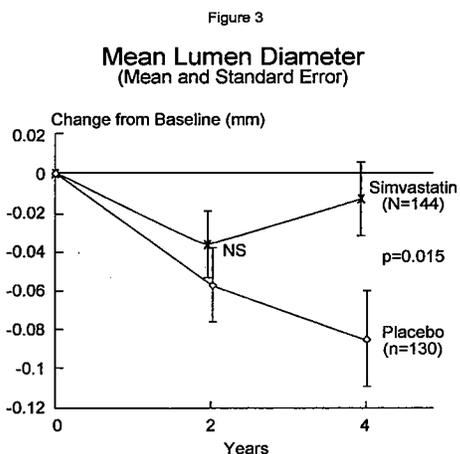
** Lijja JJ, Kivisto KT, Neuvonen PJ. Clin Pharmacol Ther 1998;64(5):477-83.

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.



Angiographic Studies

In the Multicenter Anti-Atheroma Study, the effect of therapy with simvastatin on atherosclerosis was assessed by quantitative coronary angiography in hypercholesterolemic men and women with coronary heart disease. In this randomized, double-blind, controlled study, patients with a mean baseline total-C value of 245 mg/dL (6.4 mmol/L) and a mean baseline LDL-C value of 170 mg/dL (4.4 mmol/L) were treated with conventional measures and with simvastatin 20 mg/day or placebo. Angiograms were evaluated at baseline, two and four years. A total of 347 patients had a baseline angiogram and at least one follow-up angiogram. The co-primary endpoints of the study 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 final angiogram by both these parameters (mean changes in minimum lumen diameter: -0.04 mm with simvastatin vs -0.12 mm with placebo; mean changes in mean lumen diameter: -0.03 mm with simvastatin vs -0.08 mm with placebo), as well as by change from baseline in percent diameter stenosis (0.9% simvastatin vs 3.6% placebo). After four years, the groups also differed significantly in the proportions of patients categorized with disease progression (23% simvastatin vs 33% placebo) and disease regression (18% simvastatin vs 12% placebo). In addition, simvastatin significantly decreased the proportion of patients with new lesions (13% simvastatin vs 24% placebo) and with new total occlusions (5% vs 11%). The mean change per-patient in mean and minimum lumen diameters, calculated by comparing angiograms, in the subset of 274 patients who had matched angiographic projections at baseline, two and four years is presented below (Figures 3 and 4).



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 1.

TABLE 1
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 2. 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 2
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 3. 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 3
Six-week, Lipid-lowering Effects of Simvastatin in Type III Hyperlipidemia
Median Percent Change (min,max) from Baseline

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

Homozygous Familial Hypercholesterolemia

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

Endocrine Function

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

INDICATIONS AND USAGE

Therapy with lipid-altering agents should be considered in those individuals at increased risk for atherosclerosis-related clinical events as a function of cholesterol level, the presence of CHD, or other risk factors. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol

when the response to diet and other nonpharmacological measures alone has been inadequate (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

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.

(For a discussion of efficacy results in the elderly and other pre-defined subgroups, see CLINICAL PHARMACOLOGY, *Clinical Studies*.)

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.

General Recommendations

Prior to initiating therapy with simvastatin, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, 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 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.

TABLE 4
NCEP Treatment Guidelines:
LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes
and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD [†] or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional) ^{††}
2+ Risk factors (10 year risk ≤20%)	<130	≥130	10-year risk 10-20%: ≥130 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 fibrates. 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).

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).^{***}

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

Skeletal Muscle

Simvastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as muscle pain or weakness associated with grossly elevated creatine kinase (CK) (> 10X the upper limit of normal [ULN]). **Rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, has been reported rarely.** In 4S, there was one case of myopathy among 1,399 patients taking simvastatin 20 mg and no cases among 822 patients taking 40 mg/day for a median duration of 5.4 years. In two 6-month controlled clinical studies, there was one case of myopathy among 436 patients

taking 40 mg and 5 cases among 669 patients taking 80 mg. The risk of myopathy is increased by concomitant therapy with certain drugs, some of which were excluded by the designs of these studies (see below).

Myopathy caused by drug interactions.

The incidence and severity of myopathy are increased by concomitant administration of HMG-CoA reductase inhibitors with drugs that can cause myopathy when given alone, such as gemfibrozil and other fibrates, and lipid-lowering doses (≥ 1 g/day) of niacin (nicotinic acid).

In addition, the risk of myopathy may be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Simvastatin is metabolized by the cytochrome P450 isoform 3A4 (CYP3A4). Potent inhibitors of this metabolic pathway can raise the plasma levels of HMG-CoA reductase inhibitory activity and may increase the risk of myopathy. These include cyclosporine; the azole antifungals, itraconazole and ketoconazole; the macrolide antibiotics, erythromycin and clarithromycin; HIV protease inhibitors; the antidepressant nefazodone; and large quantities of grapefruit juice (> 1 quart daily) (see below; CLINICAL PHARMACOLOGY, *Pharmacokinetics*; PRECAUTIONS, *Drug Interactions*; and DOSAGE AND ADMINISTRATION, *Dosage in Patients taking Cyclosporine*).

The risk of myopathy appears to be increased by concomitant administration of verapamil (see PRECAUTIONS, *Drug Interactions*). 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%).

Reducing the risk of myopathy.

1. General measures. Patients starting therapy with simvastatin should be advised of the risk of myopathy, and told to report promptly unexplained muscle pain, tenderness or weakness. A CK level above 10X ULN in a patient with unexplained muscle symptoms indicates myopathy. Simvastatin therapy should be discontinued if myopathy is diagnosed or suspected. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved.

Of the patients with rhabdomyolysis, many had complicated medical histories. Some had preexisting renal insufficiency, usually as a consequence of long-standing diabetes. In such patients, dose escalation requires caution. Also, as there are no known adverse consequences of brief interruption of therapy, treatment with simvastatin should be stopped a few days before elective major surgery and when any major acute medical or surgical condition supervenes.

2. Measures to reduce the risk of myopathy caused by drug interactions (see above and PRECAUTIONS, *Drug Interactions*). Physicians contemplating combined therapy with simvastatin and any of the interacting drugs should weigh the potential benefits and risks, and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent myopathy.

The combined use of simvastatin with fibrates or niacin should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination. Combinations of fibrates or niacin with low doses of simvastatin have been used without myopathy in small, short-term clinical studies with careful monitoring. Addition of these drugs to simvastatin typically provides little additional reduction in LDL-C, but further reductions of TG and further increases in HDL-C may be obtained. If one of these drugs must be used with simvastatin, clinical experience suggests that the risk of myopathy is less with niacin than with the fibrates.

In patients taking concomitant cyclosporine, fibrates or niacin, the dose of simvastatin should generally not exceed 10 mg/day (see DOSAGE AND ADMINISTRATION, *Dosage in Patients taking Cyclosporine and Concomitant Lipid-Lowering Therapy*), as the risk of myopathy increases substantially at higher doses. Concomitant use of simvastatin with itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (> 1 quart daily) is not recommended. If no alternative to a short course of treatment with itraconazole, ketoconazole, erythromycin, or clarithromycin is available, a brief suspension of simvastatin therapy during such treatment can be considered as there are no known adverse consequences to brief interruptions of long-term cholesterol-lowering therapy.

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 periodically thereafter (e.g., semiannually) for the first year of treatment or until one year after the last elevation in dose. Patients titrated to the 80-mg dose should receive an additional test at 3 months. 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 to report promptly unexplained muscle pain, tenderness, or weakness (see WARNINGS, *Skeletal Muscle*).

Drug Interactions

Gemfibrozil and other fibrates, lipid-lowering doses ($\geq 1\text{g/day}$) of niacin (nicotinic acid): These drugs increase the risk of myopathy when given concomitantly with simvastatin, probably because they can produce myopathy when given alone (see WARNINGS, *Skeletal Muscle*). There is no evidence to suggest that these agents affect the pharmacokinetics of simvastatin.

CYP3A4 Interactions: Simvastatin has no CYP3A4 inhibitory activity; therefore, it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4 (see CLINICAL PHARMACOLOGY, *Pharmacokinetics*). However, simvastatin itself is a substrate for CYP3A4. Potent inhibitors of CYP3A4 may increase the risk of myopathy by increasing the plasma concentration of HMG-CoA reductase inhibitory activity during simvastatin therapy. These inhibitors include cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, and large quantities of grapefruit juice (> 1 quart daily) (see CLINICAL PHARMACOLOGY, *Pharmacokinetics* and WARNINGS, *Skeletal Muscle*).

Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma concentrations of drugs metabolized by CYP3A4. Large quantities of grapefruit juice (> 1 quart daily) significantly increase the serum concentrations of simvastatin and its β -hydroxyacid metabolite during simvastatin therapy and should be avoided; the serum concentration of HMG-CoA reductase inhibitory activity is increased to a lesser extent (see CLINICAL PHARMACOLOGY, *Pharmacokinetics* and WARNINGS, *Skeletal Muscle*).

The risk of myopathy appears to be increased by concomitant administration of verapamil.

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

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

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

CNS Toxicity

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

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

A second two-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other HMG-CoA reductase inhibitors. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80 milligram daily dose.

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

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day, (which produces exposure levels 22 times higher than those in humans taking 80 mg/day based on surface area, mg/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 review[†] 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).

[†] 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.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Because pediatric patients are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of pediatric patients with simvastatin is not recommended at this time.

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 and other large clinical studies conducted with simvastatin, 22% of patients were elderly (1,522 of 6,985 patients were ≥ 65 years). Simvastatin significantly reduced total mortality and CHD mortality in elderly patients with a history of CHD (see CLINICAL PHARMACOLOGY). Lipid-lowering efficacy was at least as great in elderly patients compared with younger patients, and there were no overall differences in safety over the 20 to 80 mg/day dosage range.

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

Adverse experiences occurring at an incidence of 1% or greater in patients treated with ZOCOR, regardless of causality, in controlled clinical studies are shown in Table 5.

TABLE 5
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
Flatulence	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 6.

TABLE 6
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

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, *Skeletal Muscle*).

Concomitant 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 with fibrates should generally be avoided (see WARNINGS, *Skeletal Muscle*).

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

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

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving ZOCOR and should continue on this diet during treatment with ZOCOR. The dosage should be individualized according to the baseline LDL-C level, the recommended goal of therapy (see NCEP Treatment Guidelines), and the patient's response. The dosage range is 5-80 mg/day (see below).

The recommended usual starting dose is 20 mg once a day in the evening. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg/day in the evening. Adjustments of dosage should be made at intervals of 4 weeks or more. See below for dosage recommendations for patients receiving concomitant therapy with cyclosporine, fibrates or niacin, and for those with severe renal insufficiency.

Dosage in Patients with Homozygous Familial Hypercholesterolemia

Based on the results of a controlled clinical study, 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.

Dosage in Patients taking Cyclosporine

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

Concomitant Lipid-Lowering Therapy

ZOCOR is effective alone or when used concomitantly with bile-acid sequestrants. Use of ZOCOR with fibrates or niacin should generally be avoided. However, if ZOCOR is used in combination with fibrates or niacin, the dose of ZOCOR should generally not exceed 10 mg/day (see WARNINGS, *Skeletal Muscle* and PRECAUTIONS, *Drug Interactions*).

Dosage in Patients with Renal Insufficiency

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

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 0006-0735-61 unit of use bottles of 60
- 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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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 19-766/S045

MEDICAL REVIEW

REVIEW OF LABELING SUPPLEMENT

NDA 19-766/S045

Sponsor: Merck Research Laboratories

Drug Product: Zocor (simvastatin)

Date of Submission: November 8, 2000

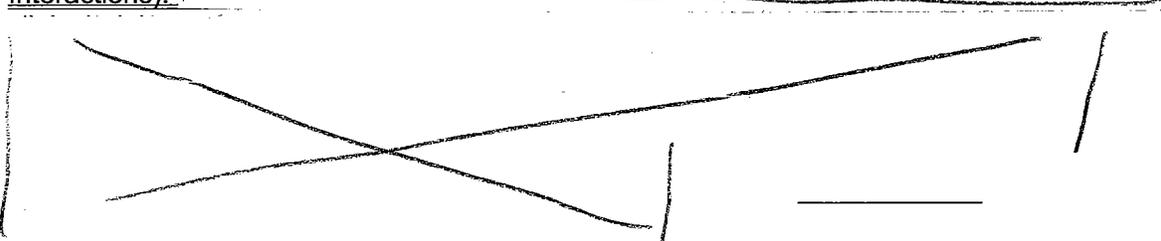
Introduction

This labeling supplement proposes to change the WARNINGS, Skeletal Muscle subsection to describe an increased risk of myopathy associated with verapamil co-administration but not with other calcium channel blockers. This information was also inserted in the PRECAUTIONS, Drug Interactions subsection. In addition, the adverse event, dermatomyositis, was added to the ADVERSE REACTIONS section of the package insert.

The specific changes to the WARNINGS and PRECAUTIONS sections are summarized as follows:

Under the WARNINGS;Skeletal Muscle subsection

The risk of myopathy appears to be increased by concomitant administration of verapamil. (see PRECAUTIONS; Drug Interactions).



Under the PRECAUTIONS section

The risk of myopathy appears to be increased by concomitant administration of verapamil.

Review of Data Submitted

Pharmacokinetic Studies

The sponsor submitted the summary results of three pharmacokinetic studies evaluating simvastatin 80 mg co-administered with one of three calcium channel blockers (CCB): diltiazem, verapamil, and amlodipine. These studies were designed to evaluate the effect of these calcium channel blockers as CYP3A4 inhibitors on the metabolism of simvastatin as measured by the total and active HMG-CoA reductase inhibitory activity.

The studies revealed that inhibitory activity of these calcium channel blockers was greatest with diltiazem > verapamil > amlodipine. Diltiazem SR 120 mg bid administered for 10 days increased the HMG-CoA reductase inhibitory activity of simvastatin 80 mg by 2.0 fold. Verapamil 240 mg SR administered for 10 days increased the HMG-CoA

reductase inhibitory activity of simvastatin 80 mg by 1.8 fold and amlodipine 10 mg administered for 10 days increased this activity by 1.3 fold.

These studies did not measure simvastatin acid (SVA) levels. Other pharmacokinetic studies evaluating effects of CYP3A4 inhibitors on simvastatin have found a higher-fold increase in simvastatin acid levels relative to inhibitory activity. The clinical relevance of reporting SVA versus inhibitory activity in these studies is debatable as the mechanism of statin-associated myopathy is not known.

Clinical Trial Data

The sponsor combined safety data from the original Integrated Summary of Safety for simvastatin, 4S, the Multicentre Anti-Atheroma Study (MAAS), the Heart Protection Study (HPS), the Study of the Effectiveness of Additional Reduction of Cholesterol and Homocysteine (SEARCH) and Dose extension program (DEP). Each of these studies varied in duration and only SEARCH and DEP contained an 80 mg treatment arm.

There were no cases of rhabdomyolysis reported in these clinical trials but several cases of myopathy defined as unexplained muscle pain or weakness with CPK levels > 10 X ULN were observed. The sponsor summarized these cases by concomitant use of verapamil, diltiazem, or amlodipine. A summary of myopathy cases without use of a CCB was also summarized. The following table lists the myopathy cases according to these categories.

Verapamil	Diltiazem	Amlodipine	No CCBs	All Patients
4/635 0.63%	2/2343 0.085%	1/1046 0.096%	13/21,224 0.061%	20/25,248 0.079%

Out of 25,248 patients treated with simvastatin at doses of 20, 40, or 80 mg, there were 20 cases of myopathy. The majority of these were not in patients receiving concomitant CCBs. The sponsor compared the incidence of myopathy in the group of patients receiving simvastatin without a CCB with the incidence of myopathy in the group of patients receiving simvastatin with either verapamil, diltiazem, and amlodipine. From this analysis they reported no difference between the incidence of myopathy associated with diltiazem and amlodipine compared to CCB use alone (0.085% and 0.096% vs 0.061%). In contrast, the incidence of myopathy in patients receiving verapamil with simvastatin was 10-fold higher than the incidence of myopathy in the simvastatin only group (0.63% vs. 0.061%; p=0.0026).

Based on these findings the sponsor concluded that despite the slightly greater pharmacokinetic interaction between diltiazem and simvastatin versus verapamil and simvastatin the clinical data suggest a greater risk of myopathy associated only with verapamil and not with diltiazem thus supporting their proposed labeling changes.

Comments on Data Submitted

From the large clinical database evaluated it is evident that the incidence of myopathy (and rhabdomyolysis) associated with simvastatin use is rare. In this particular database of over 25,000 patients the overall incidence of myopathy was less than 0.1%.

The mechanism of statin-associated myopathy and rhabdomyolysis is unknown but certain drug interactions which increase statin drug levels can increase the risk of muscle toxicity. In the case of simvastatin, a CYP3A4 substrate, the concomitant use of

potent 3A4 inhibitors significantly increase simvastatin acid levels and have been associated with both myopathy and rhabdomyolysis (the latter has only been observed in spontaneous postmarketing safety reports).

The sponsor summarized three pharmacokinetic studies of less potent CYP3A4 inhibitors (diltiazem, verapamil, and amlodipine) in this submission and noted that diltiazem increased HMG-CoA reductase inhibitory activity by 2-fold followed by 1.8-fold increase associated with verapamil and a minimal increase associated with amlodipine (1.3-fold). To determine the clinical relevance of these pK studies the sponsor evaluated the clinical trial database for concomitant CCB use. This evaluation revealed that of the 20 myopathy cases observed in 25,248 patients treated with simvastatin, 20% (4 cases) occurred with verapamil use, 10% (2 cases) occurred with diltiazem, and 0.05% (1 case) occurred with amlodipine. The majority of cases did not involve any of these CCBs (13/20; 65%).

Although verapamil is associated with more cases of myopathy in simvastatin users than the other two CCBs, there is an insufficient number of cases to conclude that diltiazem or any other CCB is not associated with myopathy. This is particularly relevant for diltiazem which demonstrated a greater pK interaction with simvastatin than verapamil plus simvastatin.

Conclusions

The observation that coadministration of verapamil with simvastatin has a higher incidence of myopathy than with simvastatin alone needs to be conveyed in the drug label. There are, however, insufficient data to conclude that such a risk is not present with combined use of simvastatin and other CCBs and such conclusions should not be made in the label.

Recommendations to the Label

The following changes are recommended to the label:

WARNINGS; Skeletal Muscle

The risk of myopathy appears to be increased by concomitant administration of verapamil (see PRECAUTIONS, Drug Interactions). 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 patients/21,224, 0.061%).

PRECAUTIONS

The risk of myopathy appears to be increased by concomitant administration of verapamil.

ADVERSE REACTIONS

The proposal to include dermatomyositis in the label is acceptable.

Recommendations to the Submission

Since the sponsor has submitted this application as a labeling supplement, changes being effected (CBE), this application should be approvable contingent upon the incorporation of FDA's recommended labeling changes. The current package insert with their proposed labeling changes will need to be withdrawn.

Mary H. Parks, MD
Medical Reviewer, HFD-510

Recommendation code: AE

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/s/

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9/18/01 09:59:42 AM
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10/3/01 05:09:11 PM
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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 19-766/S045

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Division of Metabolic and Endocrine Drug Products

Labeling Review

Application Number: 19-766/S-053; S-045

Name of Drug: Zocor (simvastatin) Tablets

Sponsor: Merck & Co.

Material Reviewed

Submission Date(s): September 14, 2001 (S-053); November 2, 2001 (email submission; S-053)
November 7, 2000 (S-045); October 3, 2001 (fax)

Background and Summary Description:

On September 17, 2001, Merck submitted a prior approval supplement (S-053) which proposes labeling changes to accommodate the recent revisions to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III) Guidelines. A revised package insert has been submitted with this supplement to reflect this change. Also, on November 8, 2000, Merck submitted a "Changes Being Effectuated" supplement (S-045) which proposed to revise the Warnings, Skeletal Muscle and Precautions sections of the package insert to include wording with respect to the increase in the risk of myopathy with verapamil. On September 25, 2001, the FDA issued an approvable letter to the firm for S-045 indicating the exact language required for approval of this supplement. The required language was submitted with the November 2, 2001, electronic amendment for S-053.

Review

The draft labeling (S-053) submitted on September 14, 2001 has been reviewed and compared to the draft labeling approved by the FDA on November 7, 2000 (S-042). In reviewing S-053, it was noted that there were numerous changes made to the package insert that were not incorporated in the approved S-042 package insert. The firm was requested to fax in justifications to verify approval of these changes. The changes and justifications are as follows:

To the Clinical Pharmacology section of the package insert, the following statement regarding triglycerides (TG) was added (*Justification: S-034/S-036, circular 7825436, approved 11/22/99*):

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.

To the Clinical Pharmacology section of the package insert, the following paragraphs regarding CYP3A4 were added (*Justification: S-039, circular 7825438, approved 8/22/00*):

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.

Simvastatin is a substrate for CYP3A4 (see PRECAUTIONS, *Drug Interactions*). Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma concentrations of drugs metabolized by CYP3A4. In one study**, 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 α -hydroxyacid metabolite [measured using a chemical assay — liquid chromatography/tandem mass spectrometry] of 16-fold and 7-fold, respectively. In a second study, 16 subjects consumed one 8 oz glass of single-strength grapefruit juice (one can of frozen concentrate diluted with 3 cans of water) with breakfast for 3 consecutive days and a single dose of 20 mg simvastatin in the evening of the third day. This regimen of grapefruit juice resulted in a mean increase in the plasma concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [using a validated enzyme inhibition assay different from that used in the first** 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.

To the Clinical Pharmacology section of the package insert, the following paragraphs have been rearranged and given subheadings (*Justification: S-034/036, circular 7825436, approved 11/22/99*):

Clinical Studies

Coronary Heart Disease

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 (Figure 1) 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]) (Figure 2) 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.

Angiographic Studies

In the Multicenter Anti-Atheroma Study, the effect of therapy with simvastatin on atherosclerosis was assessed by quantitative coronary angiography in hypercholesterolemic men and women with coronary heart disease. In this randomized, double-blind, controlled study, patients with a mean baseline total-C value of 245 mg/dL (6.4 mmol/L) and a mean baseline LDL-C value of 170 mg/dL (4.4 mmol/L) were treated with conventional measures and with simvastatin 20 mg/day or placebo. Angiograms were evaluated at baseline, two and four years. A total of 347 patients had a baseline angiogram and at least one follow-up angiogram. The co-primary endpoints of the study 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 final angiogram by both these parameters (mean changes in minimum lumen diameter: -0.04 mm with simvastatin vs -0.12 mm with placebo; mean changes in mean lumen diameter: -0.03 mm with simvastatin vs -0.08 mm with placebo), as well as by change from baseline in percent diameter stenosis (0.9% simvastatin vs 3.6% placebo). After four years, the groups also differed significantly in the proportions of patients categorized with disease progression (23% simvastatin vs 33% placebo) and disease regression (18% simvastatin vs 12% placebo). In addition, simvastatin significantly decreased the proportion of patients with new lesions (13% simvastatin vs 24% placebo) and with new total occlusions (5% vs 11%). The mean change per-patient in mean and minimum lumen diameters, calculated by comparing angiograms, in the subset of 274 patients who had matched angiographic projections at baseline, two and four years is presented below (Figures 3 and 4).

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 1.

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 2. 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.

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 3. 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.

Homozygous Familial Hypercholesterolemia

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

Endocrine Function

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

To the Clinical Pharmacology section of the package insert, the following subsection has been added (Justification: S-034/036, circular 7825436, approved 11/22/99):

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.

To the Indications and Usage section of the package insert, the following revisions regarding the NCEP guidelines were added (Basis for this supplement; S-053):

The NCEP Treatment Guidelines are summarized in Table 4:

TABLE 4
NCEP Treatment Guidelines:
LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes
and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD [†] or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional) ^{††}
2+ Risk factors (10 year risk ≤20%)	<130	≥130	10-year risk 10-20%: ≥130 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.

To the Warnings and Precautions section of the package insert, the following statements regarding verapamil have been added (*Justification; required in approvable letter for S-045 and included in S-053, awaiting approval*)

The risk of myopathy appears to be increased by concomitant administration of verapamil (see PRECAUTIONS, *Drug Interactions*). 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 appears to be increased by concomitant administration of verapamil.

To the Warnings section of the package insert, the following paragraph has been revised to read (*Justification; S-039, circular 7825438, approved 8/22/00*):

In patients taking concomitant cyclosporine, fibrates or niacin, the dose of simvastatin should generally not exceed 10 mg/day (see DOSAGE AND ADMINISTRATION, *Dosage in Patients taking Cyclosporine and Concomitant Lipid-Lowering Therapy*), as the risk of myopathy increases substantially at higher doses. Concomitant use of simvastatin with itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (> 1 quart daily) is not recommended. If no alternative to a short course of treatment with itraconazole, ketoconazole, erythromycin, or clarithromycin is available, a brief suspension of simvastatin therapy during such treatment can be considered as there are no known adverse consequences to brief interruptions of long-term cholesterol-lowering therapy.

To the Precautions section of the package insert, the following paragraphs have been added to the Drug Interactions subsection (*Justification; S-039 circular 7825438, approved 8/22/00*):

Gemfibrozil and other fibrates, lipid-lowering doses (\square 1g/day) of niacin (nicotinic acid): These drugs increase the risk of myopathy when given concomitantly with simvastatin, probably because they can produce myopathy when given alone (see WARNINGS, *Skeletal Muscle*). There is no evidence to suggest that these agents affect the pharmacokinetics of simvastatin.

CYP3A4 Interactions: Simvastatin has no CYP3A4 inhibitory activity; therefore, it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4 (see CLINICAL PHARMACOLOGY, *Pharmacokinetics*). However, simvastatin itself is a substrate for CYP3A4. Potent inhibitors of CYP3A4 may increase the risk of myopathy by increasing the plasma concentration of HMG-CoA reductase inhibitory activity during simvastatin therapy. These inhibitors include cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, and large quantities of grapefruit juice (> 1 quart daily) (see CLINICAL PHARMACOLOGY, *Pharmacokinetics* and WARNINGS, *Skeletal Muscle*). Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma concentrations of drugs metabolized by CYP3A4. Large quantities of grapefruit juice (> 1 quart daily)

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significantly increase the serum concentrations of simvastatin and its β -hydroxyacid metabolite during simvastatin therapy and should be avoided; the serum concentration of HMG-CoA reductase inhibitory activity is increased to a lesser extent (see CLINICAL PHARMACOLOGY, *Pharmacokinetics* and WARNINGS, *Skeletal Muscle*).

To the Precautions section of the package insert, the following Geriatric Use subsection has been added (Justified; S-042/S-044, 7825440, approved 11/7/00):

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 and other large clinical studies conducted with simvastatin, 22% of patients were elderly (1,522 of 6,985 patients were ≥ 65 years). Simvastatin significantly reduced total mortality and CHD mortality in elderly patients with a history of CHD (see CLINICAL PHARMACOLOGY). Lipid-lowering efficacy was at least as great in elderly patients compared with younger patients, and there were no overall differences in safety over the 20 to 80 mg/day dosage range.

To the Dosage and Administration section of the package insert, the following paragraphs should now read (Justification; S-039 circular 7825438, approved 8/22/00):

The patient should be placed on a standard cholesterol-lowering diet before receiving ZOCOR and should continue on this diet during treatment with ZOCOR. The dosage should be individualized according to the baseline LDL-C level, the recommended goal of therapy (see NCEP Treatment Guidelines), and the patient's response. The dosage range is 5-80 mg/day (see below).

The recommended usual starting dose is 20 mg once a day in the evening. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg/day in the evening. Adjustments of dosage should be made at intervals of 4 weeks or more. See below for dosage recommendations for patients receiving concomitant therapy with cyclosporine, fibrates or niacin, and for those with severe renal insufficiency.

Conclusions

The draft labeling dated November 2, 2001 (email submission), is acceptable. The package insert incorporates all previously approved labeling changes and includes the correct revisions for the NCEP Guidelines (S-053) and Risk of myopathy with regards to verapamil (S-045). An approval letter should be issued.

Reviewed by: Dwayne Keels, TIA, DMEDP (11/6/01)

Concurrence: Margaret Simoneau, R.Ph., Regulatory Project Manager (11/7/01)

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