CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 19766, S018

Trade Name: ZOCOR TABLETS

Generic Name: SIMVASTATIN

Sponsor: MERCK RESEARCH LABORATORIES

Approval Date: 5/19/97

Indication(s): LIPID ALTERING AGENT

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 19766, S018

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	Included	Pending Completion	Not Prepared	Not Required
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Chemistry Review(s)	X			
EA/FONSI	X			
Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 19766, S018

APPROVAL LETTER

MAY 19 1997

NDA 19-766/S-018

Merck Research Laboratories
Attention: Robert E. Silverman, M.D., Ph.D.
Director, Regulatory Affairs
P.O. Box 4, BLA-20
Sumneytown Pike
West Point, Pennsylvania 19486

Dear Dr. Silverman:

Please refer to your supplemental new drug application dated November 7, 1996, received November 8, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70(c) for Zocor™ (simvastatin) Tablets.

The supplemental application provides for revisions in the package insert for the following sections:

1. WARNINGS section, Skeletal Muscle subsection:

   The itraconazole text is revised to include the effect of HMG-CoA reductase inhibitors and itraconazole in patients not receiving concomitant cyclosporine.

2. PRECAUTIONS section:

   a. Drug Interactions subsection:

      The "Antipyrine" text is revised for consistency with the draft itraconazole text to suggest a potential interaction with drugs metabolized by the cytochrome P-450 enzyme system.

   b. Pediatric subsection:

      The term "children and adolescents" is replaced with "pediatric patients."

Your submission stated that these changes would be implemented on or about December 1, 1996.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling (circular 7825420) submitted on November 7, 1996. Accordingly, the supplemental application is approved effective on the date of this letter.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Margaret Simoneau, R. Ph., Project Manager, at (301) 443-3510.

Sincerely yours,

/S/ 5/18/97

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 19-766
HFD-510/Div. files
HFD-510/CSO/Simoneau
HFD-510/Orloff/Berlin
DISTRICT OFFICE
HF-2/Medwatch (with labeling plus CSO labeling review)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFI-20/Press Office (with labeling)
HFD-735/DBarash (with labeling plus CSO labeling review)
Drafted by: JRhee/May 9, 1997/ c:wpfiles/supplement/19766s18.ap
Initialed by:Galliers 5-12-97/Orloff 5-14-97/Berlin 5-13-97/SMoore 5-13-97
final: JRhee 5-15-97

SUPPLEMENT APPROVAL (AP S-018) /S/ 5-15-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19766, S018

FINAL PRINTED LABELING

7825420

MERCK & CO., INC.
West Point, PA 19486, USA

TABLETS

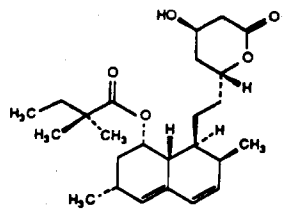
ZOCOR®

(SIMVASTATIN)

DESCRIPTION

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

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



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

Tablets ZOCOR for oral administration contain either 5 mg, 10 mg, 20 mg or 40 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 (LDL) cholesterol in atherogenesis has been well-documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological studies have established that high LDL (low-density lipoprotein) cholesterol and low HDL (high-density lipoprotein) cholesterol are both risk factors for coronary heart disease. In the Scandinavian Simvastatin Survival Study (4S), the effect of improving lipoprotein levels with ZOCOR on total mortality was assessed in 4444 patients with coronary heart disease (CHD) and baseline total cholesterol 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 cholesterol 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 cholesterol. Apolipoprotein B also falls substantially during treatment with ZOCOR. Since each LDL particle contains one molecule of apolipoprotein B, and since little apolipoprotein 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 modestly reduces VLDL cholesterol and plasma triglycerides and can produce increases of variable magnitude in HDL cholesterol. The effects of ZOCOR on Lp(a), fibrinogen, and certain other independent biochemical risk markers for coronary heart disease 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 40 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 A.H.A. recommended low-fat meal.

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).

Clinical Studies

ZOCOR has been shown to be highly effective in reducing total and LDL cholesterol 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 per 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 plasma cholesterol (TOTAL-C), LDL cholesterol (LDL-C), total cholesterol/HDL cholesterol (TOTAL-C/HDL-C) ratio, and LDL cholesterol/HDL cholesterol (LDL-C/HDL-C) ratio. ZOCOR also modestly decreased triglycerides (TRIG) and produced increases of variable magnitude in HDL cholesterol (HDL-C).

The results of a dose response study in patients with primary hypercholesterolemia are presented in Table I.

TABLE I
Dose Response in Patients with Primary Hypercholesterolemia
(Mean Percent Change from Baseline After 8 Weeks)

TREATMENT	N	TOTAL-C	LDL-C	HDL-C	LDL-C/ HDL-C	TOTAL-C/ HDL-C	TRIG.
Placebo	28	-3	-4	+2	-4	-3	+7
ZOCOR							
5 mg q.p.m.	28	-17	-24	+7	-27	-22	-10
10 mg q.p.m.	27	-24	-33	+9	-37	-29	-10
20 mg q.p.m.	26	-25	-33	+11	-36	-30	-19
40 mg q.p.m.	29	-28	-40	+12	-46	-36	-19

In the Scandinavian Simvastatin Survival Study (4S), the effect of therapy with ZOCOR on total mortality was assessed in 4444 patients with coronary heart disease (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 daily (n=2221) or placebo (n=2223) for a median duration of 5.4 years. Over the course of the study, treatment with ZOCOR led to mean reductions in total cholesterol, LDL cholesterol and triglycerides of 25%, 35%, and 10%, respectively, and a mean increase in HDL cholesterol of 8%. ZOCOR significantly reduced the risk of mortal-

ity (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). 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 patients vs 622 patients with one or more events). The risk of having a hospital-verified non-fatal MI was reduced by 37%. Furthermore, 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 patients vs 383 patients). ZOCOR reduced the risk of major coronary events to a similar extent across the range of baseline total and LDL cholesterol levels. The risk of mortality was significantly decreased in patients ≥60 years of age by 27% and in patients <60 years of age by 37%. 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 women 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.

Figure 1

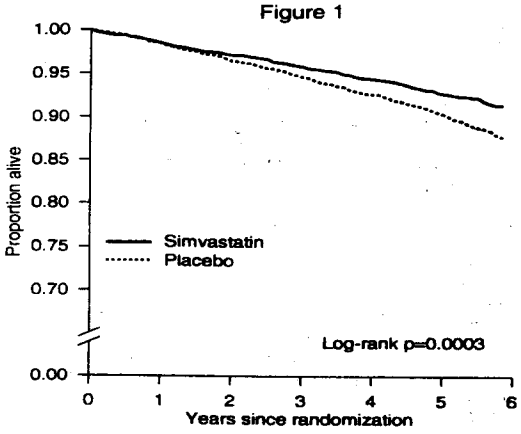
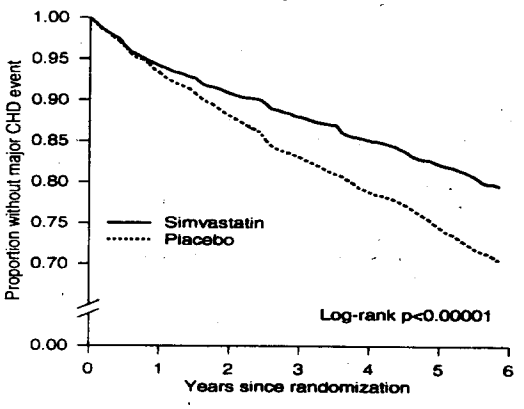


Figure 2



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 trial, patients with a mean baseline total cholesterol value of 245 mg/dL (6.4 mmol/L) and a mean baseline LDL value of 170 mg/dL (4.4 mmol/L) were treated with conventional measures and with simvastatin 20 mg/d 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 trial 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

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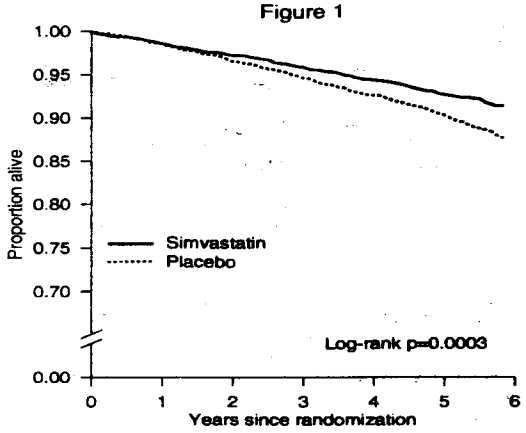
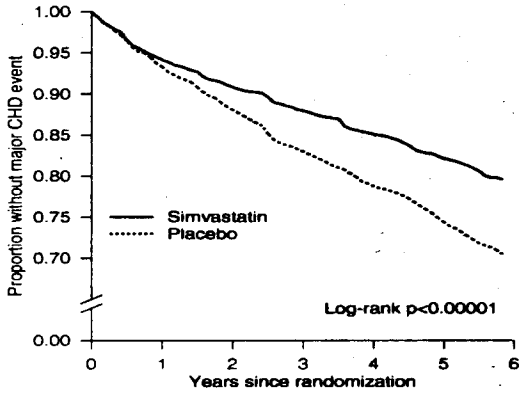


Figure 2



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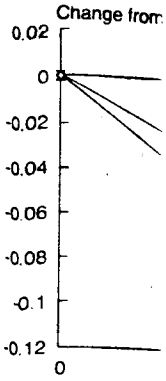

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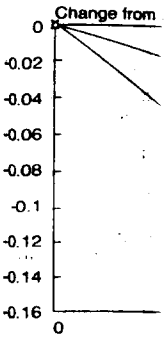

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INDICATIONS AND

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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).

Figure 3

Mean Lumen Diameter
(Mean and Standard Error)

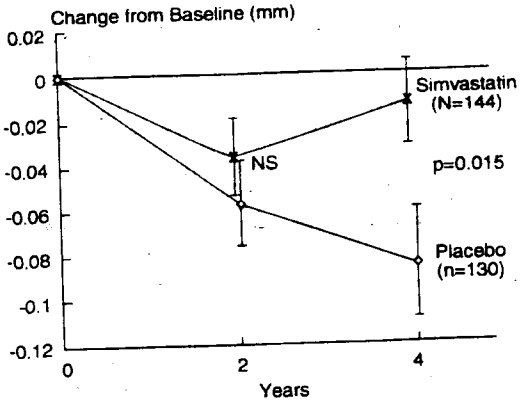
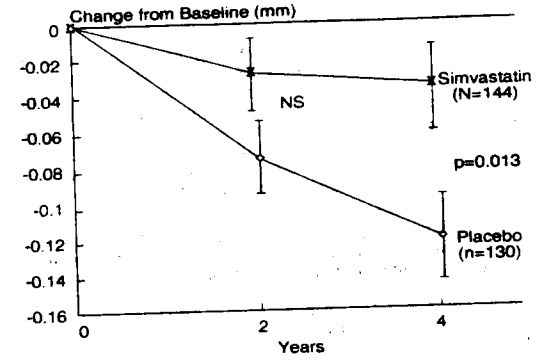


Figure 4

Minimum Lumen Diameter
(Mean and Standard Error)



In a study designed to evaluate the possible effects of simvastatin on reproductive hormones and sperm characteristics in men with familial hypercholesterolemia, there was a small decrease in the mean percentage of vital sperm and a small increase in the mean percentage of abnormal forms, with these changes achieving statistical significance at week 14. However, there was no effect on numbers or concentration of motile sperm. Simvastatin had no effect on basal reproductive hormone levels (prolactin, luteinizing hormone, follicle-stimulating hormone, and plasma testosterone). Provocative testing (HCG stimulation) was not done. Treatment with another HMG-CoA reductase inhibitor resulted in a statistically significant decrease in plasma testosterone response to HCG.

In a study to evaluate the effect of simvastatin on adrenocortical function in patients with Type II hypercholesterolemia, simvastatin had no effect on basal adrenocortical function as assessed by determination of morning plasma cortisol levels, urine free cortisol, and urinary excretion of 17-hydroxy steroids. Simvastatin also had no effect on adrenocortical reserve as evaluated by the plasma cortisol response to ACTH stimulation and insulin-induced hypoglycemia.

INDICATIONS AND USAGE

Therapy with lipid-altering agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. 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 NCEP Guidelines, below).

Coronary Heart Disease

ZOCOR® (Simvastatin)

(For a discussion of efficacy results by gender and other predefined subgroups, see CLINICAL PHARMACOLOGY, *Clinical Studies*.)

Hypercholesterolemia

ZOCOR is indicated for the reduction of elevated total and LDL cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb**).

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 triglycerides (TG). For patients with TG less than 400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation:

LDL-C = Total cholesterol – [0.20 x (triglycerides) + 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 National Cholesterol Education Program (NCEP) Treatment Guidelines are summarized below:

		LDL-Cholesterol mg/dL (mmol/L)	
Definite Atherosclerotic Disease†	Two or More Other Risk Factors††	Initiation Level	Goal
NO	NO	≥190 (≥4.9)	<160 (<4.1)
NO	YES	≥160 (≥4.1)	<130 (<3.4)
YES	YES OR NO	≥130 (≥3.4)	≤100 (≤2.6)

†Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).

††Other risk factors for coronary heart disease (CHD) include: age (males: ≥45 years; females: ≥55 years or premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension; confirmed HDL-C <35 mg/dL (<0.91 mmol/L); and diabetes mellitus. Subtract one risk factor if HDL-C is ≥60 mg/dL (≥1.6 mmol/L).

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.

Although ZOCOR may be useful to reduce elevated LDL cholesterol levels in patients with combined hypercholesterolemia and hypertriglyceridemia where hypercholesterolemia is the major abnormality (Type IIb hyperlipoproteinemia), it has not been studied in conditions where the major abnormality is elevation of chylomicrons, VLDL or IDL (i.e., hyperlipoproteinemia types I, III, IV, or 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 may cause fetal harm when administered to a pregnant woman. Therefore, simvastatin is contraindicated during pregnancy and in nursing mothers. **Simvastatin 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, simvastatin should be discontinued and the patient should be apprised of the potential hazard to the fetus.

WARNINGS

Liver Dysfunction

Persistent increases (to more than 3 times the upper limit of normal) in serum transaminases have occurred in 1% of patients who received simvastatin in clinical trials. When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pre-

**Classification of Hyperlipoproteinemias

Type	Lipoproteins elevated	Lipid Elevations major	Lipid Elevations minor
I (rare)	chylomicrons	TG	T→C
IIa	LDL	C	—
IIb	LDL VLDL	C	TG

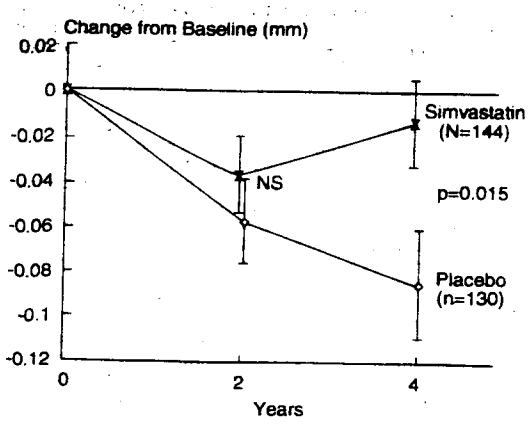
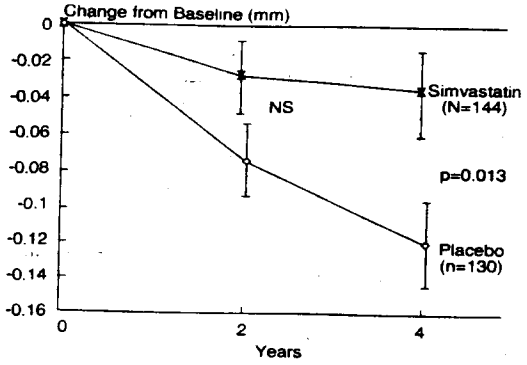


Figure 4

Minimum Lumen Diameter
(Mean and Standard Error)



In a study designed to evaluate the possible effects of simvastatin on reproductive hormones and sperm characteristics in men with familial hypercholesterolemia, there was a small decrease in the mean percentage of vital sperm and a small increase in the mean percentage of abnormal forms, with these changes achieving statistical significance at week 14. However, there was no effect on numbers or concentration of motile sperm. Simvastatin had no effect on basal reproductive hormone levels (prolactin, luteinizing hormone, follicle-stimulating hormone, and plasma testosterone). Provocative testing (HCG stimulation) was not done. Treatment with another HMG-CoA reductase inhibitor resulted in a statistically significant decrease in plasma testosterone response to HCG.

In a study to evaluate the effect of simvastatin on adrenocortical function in patients with Type II hypercholesterolemia, simvastatin had no effect on basal adrenocortical function as assessed by determination of morning plasma cortisol levels, urine free cortisol, and urinary excretion of 17-hydroxy steroids. Simvastatin also had no effect on adrenocortical reserve as evaluated by the plasma cortisol response to ACTH stimulation and insulin-induced hypoglycemia.

INDICATIONS AND USAGE

Therapy with lipid-altering agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. 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 NCEP 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.

To measure TOTAL-C, HDL-C, and triglycerides (TG). For patients with TG less than 400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation:

LDL-C = Total cholesterol – [0.20 x (triglycerides) + 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 National Cholesterol Education Program (NCEP) Treatment Guidelines are summarized below:

		LDL-Cholesterol mg/dL (mmol/L)	
Definite Atherosclerotic Disease[†]	Two or More Other Risk Factors[††]	Initiation Level	Goal
NO	NO	≥190 (≥4.9)	<160 (<4.1)
NO	YES	≥160 (≥4.1)	<130 (<3.4)
YES	YES OR NO	≥130 (≥3.4)	≤100 (≤2.6)

[†]Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).

[††]Other risk factors for coronary heart disease (CHD) include: age (males: ≥45 years; females: ≥55 years or premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension; confirmed HDL-C <35 mg/dL (<0.91 mmol/L); and diabetes mellitus. Subtract one risk factor if HDL-C is ≥60 mg/dL (≥1.6 mmol/L).

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.

Although ZOCOR may be useful to reduce elevated LDL cholesterol levels in patients with combined hypercholesterolemia and hypertriglyceridemia where hypercholesterolemia is the major abnormality (Type IIb hyperlipoproteinemia), it has not been studied in conditions where the major abnormality is elevation of chylomicrons, VLDL or IDL (i.e., hyperlipoproteinemia types I, III, IV, or 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 may cause fetal harm when administered to a pregnant woman. Therefore, simvastatin is contraindicated during pregnancy and in nursing mothers. **Simvastatin 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, simvastatin should be discontinued and the patient should be apprised of the potential hazard to the fetus.

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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.

TABLETS
ZOCOR®
(SIMVASTATIN)

treatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically thereafter (e.g., semiannually). 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 three times the upper limit of normal 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 three times the upper limit of normal) 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.

Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been associated with simvastatin therapy. Rhabdomyolysis has also been associated with other HMG-CoA reductase inhibitors when they were administered alone or concomitantly with 1) immunosuppressive therapy, including cyclosporine in cardiac transplant patients; 2) gemfibrozil or lipid-lowering doses (≥1 g/day) of nicotinic acid in non-transplant patients, or 3) erythromycin in seriously ill patients. Some of the patients who had rhabdomyolysis in association with the reductase inhibitors had pre-existing renal insufficiency, usually as a consequence of long-standing diabetes. In most subjects who have had an unsatisfactory lipid response to either simvastatin or gemfibrozil alone, the possible benefits of combined therapy with these drugs are not considered to outweigh the risk of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of simvastatin with other fibrates should generally be avoided.

Myopathy or rhabdomyolysis has occurred in transplant and non-transplant patients receiving ZOCOR or another HMG-CoA reductase inhibitor following the initiation of treatment with the antifungal agent itraconazole. In a study in normal volunteers, plasma levels of another HMG-CoA reductase inhibitor were increased about 20-fold when administered concomitantly with itraconazole. This is probably related to metabolism of both drugs by the same P-450 isoform. Based on this data, therapy with ZOCOR should be temporarily interrupted if systemic azole derivative antifungal therapy is required.

Physicians contemplating combined therapy with simvastatin and lipid-lowering doses of nicotinic acid, or with immunosuppressive drugs should carefully 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 creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Because of an apparent relationship between increased plasma levels of active metabolites derived from other HMG-CoA reductase inhibitors and myopathy, in patients taking cyclosporine, the daily dosage should not exceed 10 mg/day (see DOSAGE AND ADMINISTRATION).

Simvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Simvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

PRECAUTIONS

General

Before instituting therapy with ZOCOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Simvastatin may cause elevation of creatine phosphokinase and transaminase levels (see WARNINGS and ADVERSE

Information for Patients

Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions

Immunosuppressive Drugs, Itraconazole, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See WARNINGS, *Skeletal Muscle.*

Antipyrine: Simvastatin had no effect on the pharmacokinetics of antipyrine. However, since simvastatin is metabolized by the cytochrome P-450 isoform 3A4, this does not preclude an interaction with other drugs metabolized by the same isoform.

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.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, simvastatin was used concomitantly with angiotensin-converting enzyme (ACE) inhibitors, beta blockers, calcium-channel blockers, diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions. The effect of cholestyramine on the absorption and kinetics of simvastatin has not been determined.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. However, clinical studies have shown that simvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve, and does not reduce basal plasma testosterone concentration (see CLINICAL PHARMACOLOGY, *Clinical Studies*). Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG; the effect of simvastatin on HCG-stimulated testosterone secretion has not been studied.

Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown. Patients treated with simvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

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 44 times higher than the mean drug level in humans taking 40 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 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 hem-

[illegible] therapy or elevation in dose, and periodically thereafter (e.g., **semiannually**). 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 three times the upper limit of normal or greater persist, withdrawal of therapy with ZOCOR is recommended.

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Before instituting therapy with ZOCOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Simvastatin may cause elevation of creatine phosphokinase 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.

Homozygous Familial Hypercholesterolemia

ZOCOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have few functional LDL receptors.

Immunosuppressive Drugs, Itraconazole, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See WARNINGS, *Skeletal Muscle.*

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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 44 times higher than the mean drug level in humans taking 40 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 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 plasma drug levels that were about 50 times higher than the mean drug levels in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

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There were cataracts in female rats after two years of treatment with 50 and 100 mg/kg/day (110 and 120 times the human AUC at 40 mg/day) and in dogs in three month studies at 90 and 360 mg/kg/day and at two years at 50 mg/kg/day. These treatment levels represented plasma drug levels (AUC) of approximately 42, 40, and 26 times the mean human plasma drug exposure after a 40 milligram daily dose.

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 3, 15, and 33 times higher than the mean human plasma drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90 percent 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. Although mice were given up to 500 times the human dose (HD) on a mg/kg/body weight basis, blood levels of HMG-CoA reductase inhibitory activity were only 3-33 times higher in mice than in humans given 40 mg of ZOCOR.

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. Although mice were given up to 31 times the human dose on a mg/kg basis, plasma drug levels were only 2-4 times higher than humans given 40 mg simvastatin as measured by AUC.

In a two-year study in rats, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 45 times higher levels of simvastatin than in humans given 40 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 35 and 75 times (males) and 110 and 120 times (females) the mean human plasma drug exposure after a 40 milligram daily dose.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* 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 (15 times the maximum human exposure level, based on AUC, in patients receiving 40 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 44 times higher than those in humans taking 40 mg/day), 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 7 times the human exposure level, based on AUC, at 40 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 6 times (rat) or 4 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. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took another HMG-CoA reductase inhibitor with dextroamphetamine sulfate during the first trimester of pregnancy. Simvastatin 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. If the woman becomes pregnant while taking simvastatin, it should be discontinued and the patient advised again as to the potential

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Laboratory Tests

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A second (two-year) rat carcinogenicity study at 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 35 and 75 times (males) and 110 and 120 times (females) the mean human plasma drug exposure after a 40 milligram daily dose.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* 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 (15 times the maximum human exposure level, based on AUC, in patients receiving 40 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 44 times higher than those in humans taking 40 mg/day), 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 7 times the human exposure level, based on AUC, at 40 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 6 times (rat) or 4 times (rabbit) the human exposure based on mg/m^2 surface area. However, in studies with another structurally-related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took another HMG-CoA reductase inhibitor with dextroamphetamine sulfate during the first trimester of pregnancy. Simvastatin 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. If the woman becomes pregnant while taking simvastatin, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

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).

In the Scandinavian S
CLINICAL PHARMACOL
patients treated with 20-
cebo (n=2223), the safet
parable between group
study.

The following effects
class. Not all the effects
associated with simvast
Skeletal: muscle cramp
sis, arthralgias.
Neurological: dysfunctio
alteration of taste, imp
facial paresis), tremor, d
thesia, peripheral neur
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Hypersensitivity React
syndrome has been rep
or more of the followinc
lupus erythematous-like
vasculitis, purpura,
hemolytic anemia, posit
arthritis, arthralgia, u
fever, chills, flushing,
necrolysis, erythema
Johnson syndrome.
Gastrointestinal: pancr
active hepatitis, choles
and, rarely, cirrhosis,
hepatoma; anorexia, vo
Skin: alopecia, pruritus.
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Reproductive: gynecom
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Eye: progression of cata
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Laboratory Abnormalit
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Muscle pain or dysfun
WARNINGS, *Skeletal M*

Concomitant Therapy

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were observed. The a
limited to those repo
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OVERDOSAGE

Significant lethality v
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or dogs treated with d
No specific diagnostic
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were cataracts in female rats after two years of treatith 50 and 100 mg/kg/day (110 and 120 times the AUC at 40 mg/day) and in dogs in three month studies d 360 mg/kg/day and at two years at 50 mg/kg/day. eatment levels represented plasma drug levels (AUC) oximately 42, 40, and 26 times the mean human drug exposure after a 40 milligram daily dose.

genesis, Mutagenesis, Impairment of Fertility

'2-week carcinogenicity study, mice were adminisily doses of simvastatin of 25, 100, and 400 mg/kg eight, which resulted in mean plasma drug levels nately 3, 15, and 33 times higher than the mean plasma drug concentration (as total inhibitory activ- a 40 mg oral dose. Liver carcinomas were signifiicreased in high-dose females and mid- and highales with a maximum incidence of 90 percent in he incidence of adenomas of the liver was signifiicreased in mid- and high-dose females. Drug treatso significantly increased the incidence of lung as in mid- and high-dose males and females. Adef the Harderian gland (a gland of the eye of rodents) nificantly higher in high-dose mice than in controls. ence of a tumorigenic effect was observed at 25 mg/lthough mice were given up to 500 times the human D) on a mg/kg/body weight basis, blood levels of A reductase inhibitory activity were only 3-33 times mice than in humans given 40 mg of ZOCOR.

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o-year study in rats, there was a statistically signifiease in the incidence of thyroid follicular adenomas e rats exposed to approximately 45 times higher levnvastatin than in humans given 40 mg simvastatin ured by AUC).

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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.

ADVERSE REACTIONS

In the pre-marketing controlled clinical studies and their open extensions (2423 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 percent or greater in patients treated with ZOCOR, regardless of causality, in controlled clinical studies are shown in the table below:

	ZOCOR (N = 1583) %	Placebo (N = 157) %	Cholestyramine (N = 179) %	Probucol (N = 81) %
Body as a Whole				
Abdominal pain	3.2	3.2	8.9	2.5
Asthenia	1.6	2.5	1.1	1.2
Gastrointestinal				
Constipation	2.3	1.3	29.1	1.2
Diarrhea	1.9	2.5	7.8	3.7
Dyspepsia	1.1	—	4.5	3.7
Flatulence	1.9	1.3	14.5	6.2
Nausea	1.3	1.9	10.1	2.5
Nervous System/ Psychiatric				
Headache	3.5	5.1	4.5	3.7
Respiratory				
Upper respiratory infection	2.1	1.9	3.4	6.2

In the Scandinavian Simvastatin Survival Study (4S) (see CLINICAL PHARMACOLOGY, *Clinical Studies*) involving 4444 patients treated with 20-40 mg/day of ZOCOR (n=2221) or placebo (n=2223), the safety and tolerability profiles were comparable between groups over the median 5.4 years of the study.

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with simvastatin therapy.

Skeletal: muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, 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 creatine phosphokinase (CPK) levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CPK. 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

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 (see NCEP Treatment Guidelines for details on dietary therapy).

The recommended starting dose is 5-10 mg once a day in the evening. The recommended dosing range is 5-40 mg/day as a single dose in the evening; the maximum recommended dose is 40 mg/day. Doses should be individualized according to baseline LDL-C levels, the recommended goal of therapy (see NCEP Guidelines) and the patient's response. Patients requiring reductions in LDL cholesterol of 20% or more to achieve their goal (see INDICATIONS AND USAGE) should be started on 10 mg/day of ZOCOR. A starting dose of 5 mg should be considered for patients requiring smaller reductions and for the elderly. Adjustments of dosage should be made at intervals of 4 weeks or more.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of ZOCOR if cholesterol falls significantly below the targeted range.

In the Scandinavian Simvastatin Survival Study (4S) [see CLINICAL PHARMACOLOGY, *Clinical Studies*], patients with coronary heart disease and hypercholesterolemia were treated with a starting dose of 20 mg of ZOCOR given as a single dose in the evening.

General Recommendations

In the elderly, maximum reductions in LDL cholesterol may be achieved with daily doses of 20 mg of ZOCOR or less.

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

Concomitant Therapy

ZOCOR is effective alone or when used concomitantly with bile-acid sequestrants. Use of ZOCOR with fibrate-type drugs such as gemfibrozil or clofibrate should generally be avoided (see WARNINGS, *Skeletal Muscle*).

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 0006-0726-61 unit of use bottles of 60
(6505-01-354-4549, 5 mg 60's)
NDC 0006-0726-54 unit of use bottles of 90
(6505-01-354-4548, 5 mg 90's)
NDC 0006-0726-28 unit dose packages of 100.

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 0006-0735-61 unit of use bottles of 60
(6505-01-354-4545, 10 mg 60's)
NDC 0006-0735-54 unit of use bottles of 90
(6505-01-354-4544, 10 mg 90's)
NDC 0006-0735-28 unit dose packages of 100
(6505-01-354-4543, 10 mg individually sealed 100's)
NDC 0006-0735-82 bottles of 1000
(6505-01-373-7290, 10 mg 1000's)
NDC 0006-0735-87 bottles of 10,000
(6505-01-378-8058, 10 mg 10,000's).

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 0006-0740-61 unit of use bottles of 60
(6505-01-354-4547, 20-mg 60's)
NDC 0006-0740-82 bottles of 1000
NDC 0006-0740-87 bottles of 10,000
(6505-01-378-8771, 20 mg 10,000's).

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 0006-0749-61 unit of use bottles of 60
(6505-01-354-4546, 40 mg 60's).

Storage

Store between 5-30°C (41-86°F).

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MERCK & CO., INC., West Point, PA 19486, USA

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nancy Category X

CONTRAINDICATIONS.

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AINDICATIONS).

Gastrointestinal				
Constipation	2.3	1.3	29.1	1.2
Diarrhea	1.9	2.5	7.8	3.7
Dyspepsia	1.1	—	4.5	3.7
Flatulence	1.9	1.3	14.5	6.2
Nausea	1.3	1.9	10.1	2.5
Nervous System/ Psychiatric				
Headache	3.5	5.1	4.5	3.7
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Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, 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.

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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 creatine phosphokinase (CPK) levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CPK. 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.

ZOCOR if cholesterol falls significantly below the targeted range.

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Issued September 1996
Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19766, S018

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date NOV 18 1996

NDA No. 19-766

MERCK RESEARCH LABORATORIES
P.O. Box 4, BLA-20
Sumneytown Pike
West Point, PA 19486

Attention: Robert E. Silverman, M.D., Ph.D., Director, Regulatory Affairs

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: ZOCOR (Simvastatin)

NDA Number: 19-766

Supplement Number: S-018

Date of Supplement: November 7, 1996

Date of Receipt: November 8, 1996

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on JAN - 7 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products
Attention: Document Control Room
5600 Fishers Lane, HFD-510
Rockville, MD 20857

Sincerely yours,

/S/

Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office Drug Evaluation II
Center for Drug Evaluation and Research

NDA SUPPLEMENT ORIGINAL

Robert E. Silverman, M.D., Ph.D.
Director
Regulatory Affairs

NDA NO. 19766 REF. NO. 018
NDA SUPPL FOR SLR

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November 7, 1996

To be approved. This circular as submitted 12-5-96 /S/

MERCK
Research Laboratories

Solomon Sobel, M.D. - Director
Division of Metabolism and Endocrine
Drug Products HFD-510, Room 14B-04
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

CENTER FOR DRUG
REC'D
NOV 0 8 1996
HFD-510
EVALUATION AND RESEARCH

Noted 12-11-96 /S/ Noted 12/12/96 /S/

Dear Dr. Sobel:

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED
NDA 19-766: ZOCOR™ (Simvastatin)

Pursuant to Section 505(b) of the Food Drug and Cosmetic Act and in accordance with 21 CFR 314.70 (c), we submit a supplement to NDA 19-766.

As indicated on the attached Form FDA 356h, the supplemental application provides for changes in Item 4(c)(ii) of the approved New Drug Application for ZOCOR™.

The circular (#7825420) has been revised under WARNINGS, *Skeletal Muscle* to include new information regarding the use of HMG-CoA reductase inhibitors and itraconazole without concomitant cyclosporine as well as under PRECAUTIONS, *Drug Interactions* to suggest a potential for interactions with drugs metabolized by the cytochrome P-450 enzyme system. The PRECAUTIONS, *Pediatric Use* section has also been revised editorially to comply with the FDA final rule on pediatric labeling. Also included are a number of editorial changes to CLINICAL PHARMACOLOGY, *Clinical Studies*, INDICATIONS AND USAGE, *Hypercholesterolemia*, and HOW SUPPLIED. The following are attached:

APPR
ON

- (1) Copy of the Summary of Revisions
- (1) Copy of the draft Package Circular annotated for revisions
- (1) Copy of References
- (15) Mounted copies of printed Package Circular #7825420

The changes will become effective on or about December 1, 1996 and will apply to all packages of ZOCOR™ distributed from the company's manufacturing facilities at West Point, PA.

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

We consider the filing of this Supplemental New Drug Application to be a confidential matter, and request the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this supplemental application should be directed to Robert E. Silverman, M.D., Ph.D. (610/397-2944) or, in my absence Bonnie J. Goldmann, M.D. (610/397-2383).

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Sincerely yours,

Robert E. Silverman, M.D., Ph.D.
Director
Regulatory Affairs

Attachments

Circular # 7825420

Federal Express
Q/YARB/MUARKAMI/19-766SS

MAY 1 4 1997

Labeling Review

NDA 19-766/S-018 Zocor™ (simvastatin)

Submission date: November 7, 1996

Review date: May 9, 1997

Reviewed by: Julie Rhee, Project Manager

The package insert (circular 7825420) from 11/7/96 submission (for supplement 018) is compared against the final printed labeling (circular 7825418) for the supplement 011. The S-011 was approved 6/30/95 and the circular 7825418 was submitted 7/24/95.

I noted the following changes were made in the 11/7/96 submission (circular 7825420):

1. CLINICAL PHARMACOLOGY section, *Clinical Studies* subsection:

   In the 7/24/95 submission, an initial MI was used without spelling it out first. In the 11/7/96 submission, the sponsor made a correction and spelled it out first and then used abbreviation afterwards, i.e., myocardial infarction (MI).

   This change is acceptable.

2. WARNINGS section, *Skeletal Muscle* subsection (~~deletion~~, addition):

   "Myopathy or rhabdomyolysis has occurred in transplant . . . antifungal therapy is required."

   This supplement provides for this change.

3. PRECAUTIONS section:

   a. *Drug Interactions* subsection (~~deletion~~, addition):

      Antipyrine: ;Simvastatin had . . . of antipyrine

      However, since simvastatin is metabolized . . . other drugs metabolized by the same isoform."

      This supplement provides for this change.

b: *Pediatric Use* subsection (~~deletion~~, addition):

The reference of "children and adolescents" have been replaced with "pediatric patients" in compliance with Pediatric Use subsection under 21 CFR 201.57(f)(9).

This supplement provides for this change.

4. HOW SUPPLIED section:

A hyphen between "brick" and "red" for Zocor 40 mg tablets are removed.

This is an editorial change and is acceptable.

Recommendation:

The changes this supplement provides for are approved by Dr. Orloff.

/S/ 5-9-97
Julie Rhee
Project Manager

/S/
Enid Galliers
Chief, Project Management Staff

/S/ 5-14-97
David Orloff, M.D.
Medical Officer/Medical Team Leader

/S/ 5/13/97
William Berlin, Ph.D.
Chemist

/S/ 5/13/97
Stephen Moore, Ph.D.
Chemistry Team Leader

cc:OrigNDA
HFD-510/DivFile
HFD-510/Orloff/Berlin/Simoneau

Labeling Review