CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-766/S035

Trade Name: Zocor Tablets

Generic Name: simvastatin

Sponsor: Merck & Co., Inc.

Approval Date: September 15, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-766/S035

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APPLICATION NUMBER:

19-766/S035

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-766/S-035

SEP 15 1999

Merck & Co., Inc.
Attention: Robert E. Silverman, M.D., Ph.D.
Sumneytown Pike, BLA-10
P. O. Box 4
West Point, PA 19486

Dear Dr. Silverman:

Please refer to your supplemental new drug application dated February 16, 1999, received February 17, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zocor (simvastatin) Tablets.

We note that this supplement was submitted as a 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c).

This submission contained final printed labeling and was scheduled to be implemented on or about July 1, 1999. This supplemental new drug application provides for changes in the labeling sections of the Zocor package insert. These changes include:

1. Addition of the phrase "HIV protease inhibitors" to the drugs list in **WARNINGS**, Skeletal Muscles, Myopathy caused by drug interaction, and in **PRECAUTIONS**, Drug Interactions.

2. The four tables were editorially reformatted to one style. These revisions are found in **CLINICAL PHARMACOLOGY**, Clinical Studies; **INDICATIONS AND USAGE**, General Recommendations; and **ADVERSE REACTIONS**.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted February 16, 1999).

We note that the changes in the WARNINGS and PRECAUTIONS sections described above were incorporated in your supplemental application, S-032 (submitted on October 16, 1998) and were approved August 5, 1999. Because this supplement has been superseded by supplement-032, the FPL will not be reviewed, but will be retained in our files.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is 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 20857

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, contact Margaret Simoneau, R.Ph., Regulatory Management Officer, at (301) 827-6418.

Sincerely,

9/15/99

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

cc:
Archival NDA 19-766
HFD-510/Div. Files
HFD-510/M. Simoneau
HFD-510/Reviewers and Team Leaders
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-102/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling) - for drug discussed at advisory committee meeting.
HFD-095/DDMS-IMT (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: Mas/August 24, 1999
Initialed by:SShen8.24.99/MParks for Dorloff8.24/99/SMoore and for SKelly8.24.99/RSteigerwalt8.24.99/JWei8.24.99/EGalliers9.10.99
final:Mas9.13.99
filename: 17966.35B

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-766/S035

LABELING

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

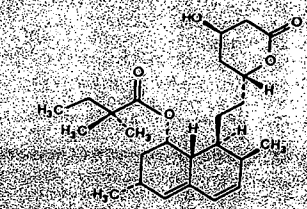
TABLETS

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



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

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

CLINICAL PHARMACOLOGY

The involvement of low density lipoprotein cholesterol (LDL-C) in atherogenesis has been well documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological studies have established that high LDL-C and low high-density lipoprotein cholesterol (HDL-C) are both risk factors for coronary heart disease. Though frequently found in association with low HDL-C, elevated plasma triglycerides (TG) have not been established as an independent risk factor for coronary heart disease (CHD). The independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

[illegible] Scandinavian Simvastatin Survival Study (4S), the

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.

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-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 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

[illegible] ZOCOR [illegible]

coronary and cardiovascular morbidity and mortality has not been determined.

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

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 3 separate studies depicting the dose response to simvastatin in patients with primary hypercholesterolemia are presented in TABLE 1.

TABLE 1.
Dose Response in Patients with Primary Hypercholesterolemia
(Mean Percent Change from Baseline After 6 to 24 Weeks)

TREATMENT	N	TOTAL-C	LDL-C	HDL-C	TG*
Lower Dose Comparative Study (Mean % Change at Week 6)					
ZOCOR					
5 mg q.p.m.	109	-19	-26	10	-12
10 mg q.p.m.	110	-23	-30	12	-15
Scandinavian Simvastatin Survival Study (Mean % Change at Week 6)					
Placebo	2223	-1	-1	0	9
ZOCOR					
20 mg q.p.m.	2221	-28	-38	8	-15
Upper Dose Comparative Study (Mean % Change averaged at Weeks 18 and 24)					
ZOCOR					
40 mg q.p.m.	433	-31	-41	9	-18
80 mg q.p.m.	664	-36	-47	8	-24

*median percent change

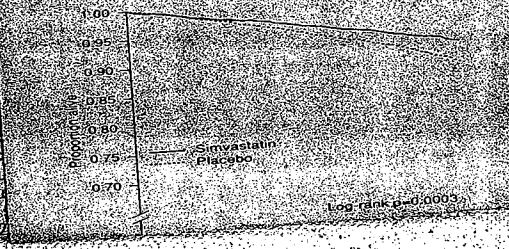
The mean reduction in LDL-C was 47% at the 80 mg dose. Of the 664 patients randomized to 80 mg, 475 patients with plasma TG ≤ 200 mg/dL had a median reduction in TG of 21%, while in 189 patients with TG > 200 mg/dL the median reduction in TG was 36%. In these studies, patients with TG > 350 mg/dL were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

In 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.

ZOCOR® (simvastatin)

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 daily (n=2,221) or placebo (n=2,223) for a median duration of 5.4 years. 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). 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%. 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). 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 patients 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. 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 63 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



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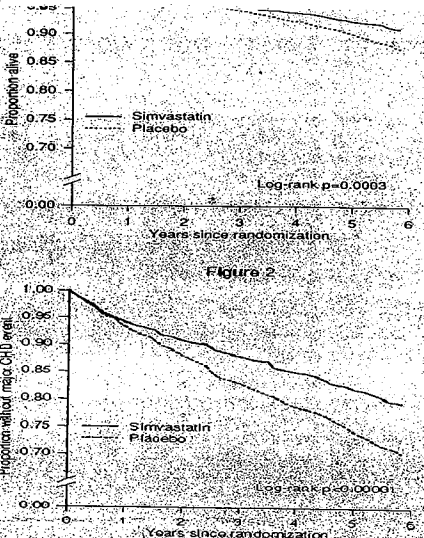

Figure 2

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 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 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 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

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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)

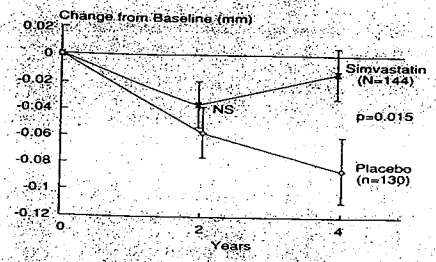
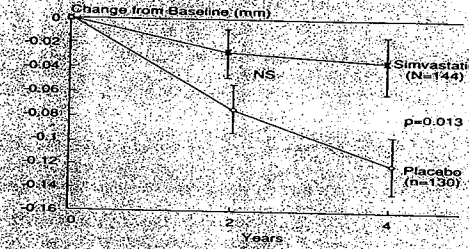


Figure 4

Minimum Lumen Diameter
(Mean and Standard Error)



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 or placebo daily 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 of any on the pituitary-gonadal axis in pre-meno-

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:

LDL-C = total-C − [0.20 x (TG) + 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 below:

NCEP Treatment Guidelines
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).

†††In CHD patients with LDL-C levels 100-129 mg/dL, the physician should exercise clinical judgment in deciding whether to initiate drug treatment.

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 hyperlipoproteinemia (where hypercholesterolemia is the major abnormality). However, it has not been studied in conditions where the major abnormality is elevation of chylomicrons, intermediate-density lipoprotein (IDL), or VLDL (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 pro-

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 by gender and other predefined subgroups, see CLINICAL PHARMACOLOGY, *Clinical Studies*.)

Hyperlipidemia

ZOCOR is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, Apo B, and TG levels in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredericksen Types IIa and IIb).

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.

*Classification of Hyperlipoproteinemias

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

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

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 child-bearing 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 daily 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 appears to be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Simvastatin is metabolized by the cytochrome P450 isoform 3A4. Certain drugs which share this metabolic pathway can raise the plasma levels of simvastatin and may increase the risk of myopathy. These include cyclosporine, itraconazole, ketoconazole and other antifungal azoles, the macrolide antibiotics erythromycin and clarithromycin, HIV protease inhibitors, and the antidepressant nefazodone.

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 unex-

plained 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 trials 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 (see DOSAGE AND ADMINISTRATION, *General Recommendations* and *Concomitant Lipid-Lowering Therapy*), as the risk of myopathy increases substantially at higher doses. Interruption of simvastatin therapy during a course of treatment with a systemic antifungal azole or a macrolide antibiotic should be considered.

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 trials. 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

tease inhibitors, Nefazodone (see WARNINGS, *Skeletal Muscle*).

Antipyrine: Simvastatin had no effect on the pharmacokinetics of antipyrine. However, since simvastatin is metabolized by the cytochrome P450 isoform 3A4, this does not preclude an interaction with other drugs metabolized by the same isoform (see WARNINGS, *Skeletal Muscle*).

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 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 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 drug levels in humans taking 80 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

dice 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

Cyclosporine, Itraconazole, Ketoconazole, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin, Clarithromycin, HIV protease 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 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 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.

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 3 times higher than humans given 80 mg simvastatin as measured by AUC).

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

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

No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to

genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

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

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS.

Safety in pregnant women has not been established.

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

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review** 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 childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

Nursing Mothers

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

Pediatric Use

Safety and effectiveness 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

serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants (see CONTRAINDICATIONS).

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 (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 percent or greater in patients treated with ZOCOR, regardless of causality, in controlled clinical studies are shown in the table below:

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

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

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.

Scandinavian Simvastatin Survival Study
Clinical Adverse Experiences

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

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

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

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 tastes, 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,

with cyclosporine, fibrates or niacin, and for those with severe renal insufficiency.

The recommended dosing range is 5-80 mg/day as a single dose in the evening. Doses should be individualized according to baseline LDL-C levels, the recommended goal of therapy (see NCEP Treatment Guidelines) and the patient's response. 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.

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.

General Recommendations

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

In patients taking cyclosporine concomitantly with simvastatin (see WARNINGS, *Skeletal Muscle*), therapy should begin with 5 mg of ZOCOR 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 not exceed 10 mg (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

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. It is not known at present if 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 usual starting dose is 20 mg once a day in the evening. Patients who require only a moderate reduction of LDL-C may be started at 10 mg. See below for dosage recommendations for patients receiving concomitant therapy.

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 0006-0740-28 unit dose packages of 100
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)

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 0006-0543-61 unit of use bottles of 60

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., West Point, PA 19486, USA

Tablets ZOCOR (simvastatin) 80 mg are manufactured for:

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

By
MERCK SHARP & DOHME LTD.
Cramlington, Northumberland, UK, NE23 9JU

Issued December 1998
Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-766/S035 `

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

MEDICAL OFFICER'S REVIEW OF SPECIAL SUPPLEMENT-CHANGES BEING EFFECTED

NDA: 19-766/S-035 **SUBMITTED: 2/16/99**
SPONSOR: MERCK RESEARCH LAB. **RECEIVED: 2/17/99**
DRUG: ZOCOR (Simvastatin) **REVIEWED: 5/6/99**

1. RESUME:

Three cases of myopathy have been reported [redacted] in patients on simvastatin and HIV protease inhibitors. The basis of this interaction is due to cytochrome P450 isoform 3A4 substrate competition between protease inhibitors and simvastatin. The greatly increased plasma concentration of simvastatin may result in myopathy (rhabdomyolysis) in sensitive patients.

II. Proposed Labeling Revision:

Add the phrase "HIV protease inhibitors" to the drugs list in **WARNINGS,** Skeletal Muscles, Myopathy caused by drug interaction, and in **PRECAUTIONS,** Drug Interactions.

III. Evaluation:

The proposed revisions in labeling are acceptable.

IV. Recommendations:

This Supplement (CBE) is approved.

S.W.Shen, M.D.
Medical Officer, HFD-510

5/6/99

D. Graham
9/13/99

CC:
Original NDA
HFD-510 Files
HFD-510-SWSHEN
HFD-510-SIMONEAU

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-766/S-035

FEB 26 1999

Merck Research Laboratories
Sumneytown Pike, P.O. Box 4 BLA-20
West Point, PA 19486

Attention: Charles L. Hyman, M.D.
Director, Regulatory Affairs

Dear Dr. Hyman:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Zocor ®(Simvastatin)
NDA Number:	19-766
Supplement Number:	S-035
Date of Supplement:	February 16, 1999
Date of Receipt:	February 17, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on April 18, 1999, 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, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

Enid Galliers

Enid Galliers
Chief, Project Management Staff
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/S-035
HFD-510/Div. Files
HFD-510/CSO/M. Simoneau

filename: C:\DATA\WPFILES\19766ACK.

SUPPLEMENT ACKNOWLEDGEMENT / CBE

Charles L. Hyman, M.D.
Director
Regulatory Affairs

ORIGINAL

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2850
215 652 5000

February 16, 1999

These copies are OFFICIAL FDA Copies not desk copies.

NDA NO. 19-766 REF NO. 035
NDA SUPPL FOR SUE

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

MERCK
Research Laboratories

Noted SE 3/1/99
See MOR

Dear Dr. Sobel:

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

Pursuant to Section 505(b) of the Food Drug and Cosmetic Act and in accordance with 21 CFR 314.70 (c)(2), we submit a supplement to NDA 19-766.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in the Labeling Section of the approved New Drug Application for ZOCOR™.

The circular (#7825433) has been revised to add the phrase "HIV protease inhibitors" to the drugs list in **WARNINGS**, *Skeletal Muscles, Myopathy caused by drug interaction,* and in **PRECAUTIONS**, *Drug Interactions*.

Also, for consistency in presentation, the four tables occurring in this circular are editorially reformatted to one style. Where appropriate, titles are added and horizontal black lines are added to set apart the table form the running text. These editorial revisions are found in **CLINICAL PHARMACOLOGY**, *Clinical Studies*; **INDICATIONS AND USAGE**, *General Recommendations*; and **ADVERSE REACTIONS.**

The following are attached to this supplement:

- One (1) copy of the Summary of Revisions
- One (1) copy of the Annotated Circular illustrating the revisions
- Twenty (20) mounted copies of the Printed Package Circular # 7825433

The changes will become effective on or about July 1, 1999 and will apply to all packages of ZOCOR™ distributed from the company's manufacturing facilities at West Point, PA.

No pushup 3/9/99

Noted 3/3/99

Please note that this circular replaces circular #7825431.

In accordance with the Food and Drug Administration Modernization Act of 1997, as indicated in the attached Form 3397, no user fee is required for this supplemental application.

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.

Merck is requesting a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.31(a). The supplement meets the requirements of a categorical exclusion under 21 CFR §25.31(a) because it will not increase the use of the active moiety, (Active Ingredient). To the best of the firm's knowledge no extraordinary circumstances exist in regards to this action.

We consider the filing of this Supplemental New Drug Application to be a confidential matter, and request 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.

Please direct questions or need for additional information to Charles L. Hyman, M.D. (610/397-2850) or, in my absence, Robert E. Silverman, M.D., Ph.D. (610/397-2944).

Sincerely,

Charles L. Hyman, M.D.
Director
Regulatory Affairs

REVIEWS COMPLETED
AP LTR 9-15-99
CSO ACTION:
☑ LETTER ☐ N.A.I. ☐ MEMO
mas 9/16/99
CSO INITIALS DATE

Attachments

Federal Express
Q\robinson\murakami\19463ss

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Merck & Co., Inc.
Sumneytown Pike, BLA-10
P. O. Box 4
West Point, PA 19486

2. TELEPHONE NUMBER *(Include Area Code)*

(610) 397-2383

3. PRODUCT NAME

ZOCOR (Simvastatin)

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER

N019766

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewir instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of informatio Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Bonnie J Goldmann	Bonnie J. Goldmann, M.D. Vice President, Domestic Liaison Regulatory Affairs	16-FEB-1999

FORM FDA 3397 (5/98)

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