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
## Contents

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 19766, S018

APPROVAL LETTER
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/ S
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/Claimen
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/

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
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 water soluble and acid labile, is hydrolyzed in the gastrointestinal tract to simvastatin acid. Simvastatin acid is oxidized in the liver to 7-(2-hydroxy-3-methylbut-2-enylidene)chroman-4-one, a compound known as mevalonic acid (MVA) O-hydratase. This enzyme catalyzes the conversion of MVA to mevalonic acid, which is an early and non-limiting step in the biosynthesis of cholesterol.

**CLINICAL PHARMACOLOGY**
The mechanism of action of ZOCOR® (Simvastatin) in hypercholesterolemic patients is currently unknown. It is believed that ZOCOR® decreases cholesterol synthesis by competitively inhibiting HMG-CoA reductase, an enzyme that catalyzes the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonic acid. ZOCOR® is well absorbed after oral administration. The amount of simvastatin acid that is absorbed into the bloodstream is small, and the extent of absorption is not dose-related. The main route of elimination is via the bile, and the drug is excreted in the feces. Simvastatin acid is not biotransformed to other metabolites or excreted in the urine. Simvastatin acid is a weak acid, with a pKa value of 2.5.

**PHARMACOKINETICS**
Simvastatin is a white to off-white, amorphous, crystalline powder that is practically insoluble in water and methanol in chloroform, methanol, and ethanol. Tablets ZOCOR® for oral administration contain either 5 mg, 10 mg, or 20 mg of simvastatin and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, stearic acid, sodium lauryl sulfate, magnesium stearate, and silicon dioxide. The tablets are tan in color and may contain the following dyes: red iron oxide, yellow iron oxide, and blue lake pigment. Tablets ZOCOR® contain 22 mg of lactose monohydrate per 5 mg tablet, 43 mg of lactose monohydrate per 10 mg tablet, and 85 mg of lactose monohydrate per 20 mg tablet.

**CONTRAINDICATIONS**
Contraindications include the use of ZOCOR® in patients with a history of liver disease or in patients with a history of myopathy.

**PHARMACOLOGY**
Simvastatin is a competitive inhibitor of HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonic acid. It has a high affinity for the enzyme and is selectively taken up by the liver. This property leads to a selective decrease in the production of cholesterol in the liver. Simvastatin also decreases cholesterol synthesis in the intestine and increases cholesterol excretion in the bile. It is believed that these effects are responsible for the reduction in blood cholesterol levels.

**ADVERSE REACTIONS**
Adverse reactions associated with ZOCOR® include hepatic effects, gastrointestinal effects, and dermatologic effects. Hepatic effects include elevations in serum transaminases, which are usually asymptomatic. Gastrointestinal effects include nausea, diarrhea, constipation, and abdominal pain. Dermatologic effects include rash, pruritus, and alopecia.

**INTERACTIONS**
ZOCOR® interacts with a variety of drugs that may affect cholesterol levels, such as rifampin, cyclosporine, and azole antifungal agents. Simvastatin is a substrate for CYP3A4, and it may interact with other drugs that are also substrates for this enzyme. ZOCOR® may also interact with drugs that are excreted in the bile, such as amphotericin B and lovastatin.

**DOSE AND ADMINISTRATION**
The recommended dosage of ZOCOR® is 10 mg orally once daily. The dosage may be increased to 20 mg orally once daily if needed.

**PRECAUTIONS**
ZOCOR® should not be used in patients with a history of liver disease or in patients with a history of myopathy. It is important to monitor patients for signs of liver disease, such as elevations in serum transaminases. ZOCOR® should be administered with caution to patients with pre-existing liver disease.

**NURSING CONSIDERATIONS**
ZOCOR® should be administered with caution to patients with pre-existing liver disease. Nursing considerations include monitoring for signs of liver disease, such as elevations in serum transaminases.

**REFERENCES**
For a complete list of references, please refer to the prescribing information for ZOCOR®.

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**IN THE SCIENTIFIC LITERATURE**
The effects of ZOCOR® on total cholesterol levels were studied in patients with hypercholesterolemia. The study was designed in a single-blind, parallel-group, randomized, placebo-controlled trial. The study was conducted in a single-center, multicenter, randomized, placebo-controlled trial. Patients were randomized to receive either ZOCOR® or placebo for 12 weeks. The primary endpoint was the percentage change in total cholesterol levels from baseline to week 12.
In the Multicenter Anti-Atheroma Study, the effect of therapy with simvastatin on atherosclerosis was assessed by quantifying coronary angiography in hypercholesterolemic men and women with coronary heart disease. In this randomized, double-blind, controlled trial, patients with a mean baseline 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/dl 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 primary endpoints of the trial were mean changes 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: -0.05 mm with simvastatin vs. -0.03 mm with placebo).
In the Multicenter Anti-Atheroma Study, the effect of therapy with simvastatin on atheroerosion 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 246 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 local and diffuse disease, respectively. Simvastatin significantly slowed the progression of lesions as measured in the final angiogram by both these parameters (mean change in minimum lumen diameter -0.04 mm with simvastatin vs -0.12 mm with placebo, mean change in mean lumen diameter -0.03 mm with simvastatin vs -0.08 mm with placebo), as well as by changes based on percentages (0.3% simvastatin vs 3.8% placebo). After four years, the groups also differed significantly in the proportions of patients categorized with disease progression (22% simvastatin vs 33% placebo) and disease regression (18% simvastatin vs 12% placebo). In addition, simvastatin significantly decreased the
ZOCOR® (Simvastatin)

(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, such as diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, and other drugs therapy, 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:

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

For TG levels ≤400 mg/dL (<4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In such cases, ZOCOR® may be low or normal despite elevated patients.

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. If the LDL-C levels are not available, then the TOTAL-C levels can be used to monitor treatment.

Although ZOCOR® may be used 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 specifically studied in conditions where the major abnormality is elevation of chylomicrons, VLDL, or IDL (i.e., Type IV hyperlipoproteinemia or Type IIa, IIb, or IIc).

**Contraindications**

Hypersensitivity to any component of this medication.

**Warnings**

**Liver Dysfunction**

Persistent increase in transaminase levels over 3 times the upper limit of normal in serum transaminases have occurred in some patients. In patients who received simvastatin in clinical trials, serious liver enzyme elevations have occurred. If liver enzymes exceed 3-fold normal, ZOCOR® should be discontinued and the patient should be assessed for the potential hazard to the fetus.

** беременные и кормящие**

Pregnancy and lactation. In pregnant women and animals, there is no evidence of harm to the fetus or baby. However, breastfeeding mothers should not breastfeed their infants for 2 weeks after discontinuing ZOCOR®.

**Clinical Studies**

**Diagnosis of Hypocholesterolemia**

**Classification of Hypocholesterolemia**

**Lipid Elevations**

**Lipoprotein**

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**Coronary Heart Disease**

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 viable 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 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 salivary cortisol, 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 a multiple risk factor intervention in these individuals at significant increased risk for atherosclerotic vascular disease due to primary hypercholesterolemia. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when the plasma cholesterol levels in the other nonpharmacologic regimens alone have been inadequate (see NCEP Guidelines, below).
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 viable 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.

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.

LDL-C = Total cholesterol – (10 x triglycerides + HDL-C)

For TG levels >400 mg/dL, (>4.6 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 recommended.

Lipid determinations should be performed at intervals of no less than 4 weeks and dosage adjusted according to the patient's response to therapy.

The National Cholesterol Education Program (NCEP) Treatment Guidelines are summarized below:

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*Coronary heart disease or peripheral vascular disease including symptoms of coronary artery disease

**Other risk factors for coronary heart disease include age: male >45 years; female >55 years; obesity; or premature menopause without estrogen replacement therapy; family history of premature CAD; current cigarette smoking; hypertension; confirmed one risk factor if HDL-C is <40 mg/dL, or <1.0 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 level be used to monitor treatment.

Although ZOCOR has been shown to reduce elevated LDL cholesterol levels in patients with combined hypercholesterolemia and hypertriglyceridemia, hypercholesterolemia is the major abnormality (Type IIb hyperlipoproteinemia), it has not been studied in conditions where major abnormality is elevation of chylomicrons, VLDL, or LDL, i.e., hypercholesterolemia types I, IIa, IV, or VI.*

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 in women who are or may become pregnant, or while nursing. 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 simvastatin, the drug should be discontinued and the patient should be apprised of the potential for harm to the fetus. WARNINGS

Liver Dysfunction
Persistence in 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-
ZOCOR® (Simvastatin)


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

It is recommended that liver function tests be performed before the initiation of treatment, and 6 and 12 weeks after initiation of therapy or every 6 months thereafter (e.g., semiannually). Patients who have 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 abnormalities return to normal. Should an increase in ALT or AST of more than twice the upper limit of normal persist, withdrawal of therapy with ZOCOR is recommended.

When 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 and were usually transitory. Transaminase changes were also observed in 2.6% of patients who 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 myopathy have been associated with simvastatin therapy. Rhabdomyolysis has also been associated with other lipid-lowering agents that are administered alone or concomitantly with other lipid-lowering therapies. Patients should be advised to report the following symptoms immediately: muscle tenderness, muscle weakness, darkening of urine, and muscle pain or cramps. In most subjects who have had an unsatisfactory lipid response to either simvastatin or a statin alone, it has been possible to achieve the appropriate combination therapy with these drugs are not considered to outweigh the risk of severe myopathy, rhabdomyolysis, and acute renal failure. However, in those instances in which the interaction occurs with statins other than gemfibrozil, myopathy and/or rhabdomyolysis have been reported to occur in association with the use of other fibrates alone, including clofibrate. Therefore, the concomitant use of simvastatin with other fibrates should generally be avoided.

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

When simvastatin is combined with 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 adverse effects such as myopathy, rhabdomyolysis, tenderness, or weakness, particularly during the initial months of therapy and any period of upward dosage titration or other 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, in patients taking cyclosporine, the daily dosage should not exceed 10 mg/day of ZOCOR. Other HMG-CoA reductase inhibitors have been reported to increase the CPK levels in patients on corticosteroids. 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 any patient with an elevated blood pressure with appropriate diet, exercise, and weight reduction in obese patients, and to correct any underlying metabolic or other medical problems (see INDICATIONS AND USAGE). Simvastatin may cause elevation of creatine phosphokinase and transaminase levels (see WARNINGS and ADVERSE

7826420

ZOCOR® (Simvastatin)

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

Immuno-suppressant drugs: Tetracyclines, Gemfibrozil, Niacin (Nicotinic Acid), Ethinylene: See WARNINGS, Skeletal Muscle: Antineoplastic: Simvastatin had no effect on the pharmacokinetics of antineoplastic agents. 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 Cmax, but no change in AUC. The peak serum total and active inhibitors with concomitant administration of anticoagulants such as ZOCOR and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.

Dexigem: Concomitant administration of a single dose of dexigem in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 mg/mL) in dexigem concentrations in plasma (as measured by a radiometric homolog) when compared to concomitant administration of placebo and dexigem. Patients taking dexigem 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 mg/day reduced the effect of warfarin on prothrombin time by 25% in volunteers and 4-5% in the patient volunteers studied, respectively. In patients with HMG-CoA reductase inhibitors, evidence of bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly with simvastatin. The prothrombin time should be determined before starting simvastatin and frequently enough thereafter to insure that no important alteration of prothrombin time occurs. Once a stable prothrombin time has been determined, 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 coumarin anticoagulants.

Other Concomitant Therapy: Although specific interaction data were not performed, in clinical studies, simvastatin was used concomitantly with angiotensin converting enzyme (ACE) inhibitors, beta blockers, calcium-channel blockers, diuretics, and oral or parenteral anticoagulant 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 absorption and synthesis and may slightly blunt adrenal and/or gonadal steroid production. However, studies have shown that simvastatin does not reduce basal plasma cortisol concentrations in normal volunteers. Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone concentrations in men and affect 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 secretion. There is no controlled clinical evidence on the effect of simvastatin on male fertility and no studies have been conducted in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown. Patients receiving 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 cholesterol lowering agent is administered to patients also receiving other drugs (e.g., estrogen, beta blockers, corticosteroids) 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 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total plasma inhibitory activity). This same drug also produced moderately severe optic nerve degeneration, retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that produced a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions characterized by perivascular hyp
null
There were cataracts in female rats after two years of treatment with 50 and 100 mg/kg/day and in males at 100, 10, and 400 mg/kg/day and in dogs in three month studies on the human. Changes were observed at 90 and 360 mg/kg/day and at two years at 90 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 1.5, 19, and 31 times higher than the mean human plasma drug concentration in the absence of inhibitors. Liver carcinomas were significantly increased in high-dose females and mid-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 only. No evidence of a tumorigenic effect was observed at 25 mg/kg/day. No tumors were given up to 500 mg/kg/day in 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 humans than in humans given 40 mg of simvastatin as measured by AUC.

In a separate 52-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 carcinomas 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 25 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 the rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an in vitro clastogenic 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 the repeated fertility study in which simvastatin was administered at the same dose level to male rats for 11 weeks (the entire estrous 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 produced an AUC approximately 44 times higher than those in humans taking 40 mg/day, seminiferous tubule degeneration (microsis) and loss of spermatogonia (epididymal maturation) were observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, 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 75 mg/kg/day or in rabbits at doses up to 10 mg/kg daily. These results resulted in 6 times rats or 4 times (305) the human exposure based on body surface area. However, in studies with another structure-activity-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 bone defect, Meckel's esophageal fistula, and atrial asplenia (WATER association) in a baby born to a woman who took another HMG-CoA reductase inhibitor with drosoglucosamine 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, it should be discontinued and the patient advised again as to the potential

ADVERSE REACTIONS

In the pre-mark presentation (1:2 of approximate 1000 patients) adverse reactions have been reported in more than 200 patients.

In the Sandin study, adverse events were observed in approximately 22.2% of patients taking simvastatin. The most common adverse event was constipation, occurring in approximately 6% of patients taking simvastatin. In the Concomitant 17 study, the most common adverse event was constipation, occurring in approximately 6% of patients taking simvastatin.
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 appeared to be consistent with findings from other HMG-CoA reductase inhibitors. These treatment levels represented plasma drug levels (AUC) of approximately 25 and 75 times (males) and 110 and 120 times (females) the mean human plasma drug exposure after a 40 mg/day oral 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 chromosomal 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 the 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, (which produces exposure levels 44 times higher than those in humans taking 40 mg/day), seminiferous tubule degeneration (incratification and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermaticcylc 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/day. These doses resulted in 6 times (rat) or 4 times (rabbit) the human exposure (AUC) of 40 mg/day. However, in studies with another structurally-related HMG-CoA reductase inhibitor, statin-related embryotoxications were observed in rats and mice. Rare reports of congenital anomalies have been received following maternal exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony dysplasia, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took another HMG-CoA reductase inhibitor with oxymetholone therapy late 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).
were caterpillars in female rats after two years of treat-
ment with 50 and 100 mg/kg/day (110 and 120 calories/day for 300 days) [110, 120]. The highest dose of 360 mg/kg/day and at 50 and 100 mg/kg/day, oestrogen levels represented plasma testosterone (T) and estradiol (E2) and were within the normal human drug exposure after a 40 milligram daily dose.

reness, Mutagenesis, Impairment of Fertility

2-week carcinogenicity study, mice were adminis-
tered a dose of simvastatin of 25, 50 or 100 mg/kg, which resulted in mean plasma drug levels of 100, 300 and 600 mg/kg, respectively. The drug concentration increased in high-dose males and mid- and high-dose females with a maximum incidence of 90 percent in the incidence of adenocarcinoma (liver) was significant increased in mid- and high-dose females. Drug treat-
ment significantly increased the incidence of liver adenocarcinoma (liver) in both males and females. Ade-
quate and hardening of the liver was significant in females. Significantly, a single dose of ZOCOR was able to separate 92-week carcinogenicity study in mice at 100 mg/kg, but not the 25 mg/kg group. Although mice were given up to 31 times the dose on a mg/kg basis, drug plasma levels were only significantly higher than human given 40 mg simvastatin as in a 40 milligram daily dose.

Another study in rats, there was a statistically signifi-
cance in the incidence of thyroid follicular adenomas in rats exposed to approximately 49 mg simvastatin per kg body wt (12). However, in rats, there was a significant toxicity at 25 mg/kg (12).

in the 2-year rat carcinogenicit study with doses of 30 mg/kg/day product simvastatin (AUC) and the same dose in females at both doses and in males at 100 mg/kg/day with lu- men was within the normal human body weight. The AUC (UC) at approximately 35 and 75 times imales and 120 times (females) less than the maximum plasma level of simvastatin after a 40 milligram daily dose.

The incidence of mutagenicity was observed in a micro-
bial assay testing mutants strains of Salmonella typhi-
murium. No evidence of damage to genetic material was detected. In the study, a single dose of simvastatin at up to 79 mmol cell generation was studied using a more viral or amnion assay in mouse bone marrow. 

was decreased fertility in male rats treated with sim-
vastatin at 30 mg/kg/day (6). In addition, the effects of simvastatin on the testes in male rats were significant decreased (7). Simvastatin was studied in a in a study in rats (20). No oocyte abnormal assay in mouse bone marrow. 

in drug related testicular atrophy, decreased sperm count and testicular degeneration at 10 mg/kg/day, (approximately 7 times the human dose). The study concluded that simvastatin is not a reproductive endpoint.

The study concluded that simvastatin is not a reproductive endpoint.

 inneficiency of disulfiram.
In the Scandinavian Simvastatin Survival Study (45) see CLINICAL PHARMACOLOGY, Clinical Studies, patients with coronary heart disease and hypercholesterolemia were treated with a starting dose of 20 mg ZOCOR as given in 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 (see WARNINGS, Skeletal Muscle).

How Supplied
No. 358 — 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 0065-01-354-454, 5 mg (500)
No. 358b — Tablets ZOCOR 10 mg are peach, shield-shaped, film-coated tablets, coded MSD 751 on one side and ZOCOR on the other. They are supplied as follows: NDC 0065-01-354-454, 10 mg (500) and NDC 0065-01-354-454, 20 mg (500) and NDC 0065-01-354-454, 5 mg (500)
No. 359 — Tablets ZOCOR 20 mg are brick red, shield-shaped, film-coated tablets, coded MSD 740 on one side and ZOCOR on the other. They are supplied as follows: NDC 0065-01-354-454, 20 mg (500)
No. 359b — Tablets ZOCOR 30 mg are tan, shield-shaped, film-coated tablets, coded MSD 772 on one side and ZOCOR on the other. They are supplied as follows: NDC 0065-01-354-454, 30 mg (400)
No. 359c — Tablets ZOCOR 40 mg are brick red, shield-shaped, film-coated tablets, coded MSD 772 on one side and ZOCOR on the other. They are supplied as follows: NDC 0065-01-354-454, 40 mg (400)

Storage
Store between 2-5°C (36-41°F)

Issued September 1996
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19766, S018

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE
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 Numbers: 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-810
Rockville, MD 20857

Sincerely yours,

/\n
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
November 7, 1996

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

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:

- (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).

Sincerely yours,

[Signature]

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

Attachments

Circular # 7825420

Federal Express
QYARBM/AAJAMZ%76655
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. \textit{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.

\textit{/S/} \textit{5-9-97}  
[Julie Rhee]  
Project Manager

\textit{/S/}  
[Enid Galliers]  
Chief, Project Management Staff

\textit{/S/} \textit{5-14-97}  
[David Orloff, M.D.]  
Medical Officer/Medical Team Leader

\textit{/S/} \textit{5-13-97}  
[Stephen Moore, Ph.D.]  
Chemistry Team Leader

\textit{cc:OrigNDA}  
HFD-510/DivFile  
HFD-510/Orloff/Berlin/Simoneau

Labeling Review