CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-766/S014

Trade Name: Zocor Tablets

Generic Name: Simvastatin

Sponsor: Meck & Co, Inc.

Approval Date: June 9, 1995

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-766/S014

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APPLICATION NUMBER:

19-766/S014

APPROVAL LETTER

NDA 19-766/S-014

ORIGINAL

Merck & Co., Inc.
Attention: Robert Silverman, M.D., Ph.D.
Director, Regulatory Affairs
BLA-30
WEST POINT PA 19486

JUN - 9 1995

Dear Dr. Silverman:

Please refer to your May 9, 1995, supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zocor (simvastatin) Tablets.

This supplemental application, "Special Supplement - Changes Being Effected," provides for revisions, including editorial revisions, in the package insert in the following sections:

1. WARNINGS

   Under the Liver Dysfunction and Skeletal Muscle headings - to include editorial revisions.

2. PRECAUTIONS

   a. Under the "Warfarin" heading in the Drug Interactions subsection - to include data from the Oxford Pilot study regarding increase in prothrombin time.

   b. In the Carcinogenesis, Mutagenesis, Impairment of Fertility subsection - to include an editorial revision.

3. HOW SUPPLIED

   To state that tablets are coded with "ZOCOR" on one side.

We have completed our 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 May 9, 1995, final printed labeling. Accordingly, the supplemental application is approved.

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

Should you have any questions, please contact:

Stephen T. Trostle
Consumer Safety Officer
Telephone: 301-443-3520.

Sincerely yours,

6/9/95

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

cc:

Original NDA
DISTRICT OFFICE (with labeling)
HF-2/MEDWATCH (with labeling)
HFD-85 (with labeling)
HFD-240 (with labeling)
HFD-638 (with labeling)
HFD-735/DBarash (with labeling)
HFD-510
HFD-510/SAurecchia/WBerlin/EBarbehenn
HFD-510/STrostle/06/01/95/ft/stt/06/09/95 \N19766AP.014
ST 06/09/95

Section affected: WARNINGS
PRECAUTIONS
HOW SUPPLIED

Concurrence: EBarbehenn, AJordan 06.02; WBerlin 06.05; YCHiu 06.07;
SAurecchia, GTroendle, EGalliers 06.08.95

SUPPLEMENT APPROVAL (AP: NDA 19-766/S-014)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-766/S014

LABELING

APPROVED JUN - 9 1995

7825414

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

TABLETS

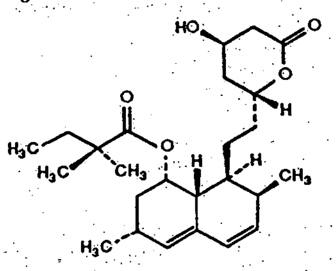
ZOCOR®

(SIMVASTATIN)

DESCRIPTION

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

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



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

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

CLINICAL PHARMACOLOGY

The involvement of low-density lipoprotein (LDL) cholesterol in atherogenesis has been well-documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological studies have established that high LDL (low-density lipoprotein) cholesterol and low HDL (high-density lipoprotein) cholesterol are both risk factors for coronary heart disease. The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), coordinated by the National Institutes of Health (NIH), studied men aged 35-59 with total cholesterol levels of 265 mg/dL (6.8 mmol/L) or greater, LDL cholesterol values 175 mg/dL (4.5 mmol/L) or greater, and triglyceride levels not more than 300 mg/dL (3.4 mmol/L). This seven-year, double-blind, placebo-con-

base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin.

Following an oral dose of ^{14}C-labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug. Plasma concentrations of total radioactivity (simvastatin plus ^{14}C-metabolites) peaked at 4 hours and declined rapidly to about 10% of peak by 12 hours postdose. Absorption of simvastatin, estimated relative to an intravenous reference dose, in each of two animal species tested, averaged about 85% of an oral dose. In animal studies, after oral dosing, simvastatin achieved substantially higher concentrations in the liver than in non-target tissues. Simvastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of simvastatin (estimated to be >60% in man), the availability of drug to the general circulation is low. In a single-dose study in nine healthy subjects, it was estimated that less than 5% of an oral dose of simvastatin reaches the general circulation as active inhibitors. Following administration of simvastatin tablets, the coefficient of variation, based on between-subject variability, was approximately 48% for the area under the concentration-time curve (AUC) for total inhibitory activity in the general circulation.

Both simvastatin and its β-hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins. Animal studies have not been performed to determine whether simvastatin crosses the blood-brain and placental barriers. However, when radiolabeled simvastatin was administered to rats, simvastatin-derived radioactivity crossed the blood-brain barrier.

The major active metabolites of simvastatin present in human plasma are the β-hydroxyacid of simvastatin and its 6'-hydroxy, 6'-hydroxymethyl, and 6'-exomethylene derivatives. Peak plasma concentrations of both active and total inhibitors were attained within 1.3 to 2.4 hours postdose. While the recommended therapeutic dose range is 5 to 40 mg/day, there was no substantial deviation from linearity of AUC of inhibitors in the general circulation with an increase in dose to as high as 120 mg. Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before an A.H.A. recommended low-fat meal.

Kinetic studies with another reductase inhibitor, having a similar principal route of elimination, have suggested that for a given dose level higher systemic exposure may be achieved in patients with severe renal insufficiency (as measured by creatinine clearance).

Clinical Studies

ZOCOR has been shown to be highly effective in reducing total and LDL cholesterol in heterozygous familial and non-familial forms of hypercholesterolemia and in mixed hyperlipidemia. A marked response was seen within 2 weeks, and the maximum therapeutic response occurred within 4-6 weeks. The response was maintained during chronic therapy.

In a multicenter, double-blind, placebo-controlled, dose-response study in patients with familial or non-familial hypercholesterolemia, ZOCOR given as a single dose in the evening (the recommended dosing) was similarly effective as when given on a twice-daily basis. ZOCOR consistently and significantly decreased total plasma cholesterol (TOTAL-C), LDL cholesterol (LDL-C), total cholesterol/HDL cholesterol (TOTAL-C/HDL-C) ratio, and LDL cholesterol/HDL cholesterol (LDL-C/HDL-C) ratio. ZOCOR also modestly decreased triglycerides (TRIG) and produced increases of variable magnitude in HDL cholesterol (HDL-C).

density lipoprotein) cholesterol are both risk factors for coronary heart disease. The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), coordinated by the National Institutes of Health (NIH), studied men aged 35-59 with total cholesterol levels of 265 mg/dL (6.8 mmol/L) or greater, LDL cholesterol values 175 mg/dL (4.5 mmol/L) or greater, and triglyceride levels not more than 300 mg/dL (3.4 mmol/L). This seven-year, double-blind, placebo-controlled study demonstrated that lowering LDL cholesterol with diet and cholestyramine decreased the combined rate of coronary heart disease death plus non-fatal myocardial infarction.

ZOCOR has been shown to reduce both normal and elevated LDL cholesterol concentrations. The effect of simvastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity or mortality has not been established.

LDL is formed from very-low-density lipoprotein (VLDL) and is catabolized predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of ZOCOR may involve both reduction of VLDL cholesterol concentration, and induction of the LDL receptor, leading to reduced production and/or increased catabolism of LDL cholesterol. Apolipoprotein B also falls substantially during treatment with ZOCOR. Since each LDL particle contains one molecule of apolipoprotein B, and since little apolipoprotein B is found in other lipoproteins, this strongly suggests that ZOCOR does not merely cause cholesterol to be lost from LDL, but also reduces the concentration of circulating LDL particles. In addition, ZOCOR modestly reduces VLDL cholesterol and plasma triglycerides and can produce increases of variable magnitude in HDL cholesterol. The effects of ZOCOR on Lp(a), fibrinogen, and certain other independent biochemical risk markers for coronary heart disease are unknown.

ZOCOR is a specific inhibitor of HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate. The conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol.

Pharmacokinetics

Simvastatin is a lactone that is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the β-hydroxyacid metabolites (active inhibitors) and, following evening the recommended dosing) when given on a twice-daily basis. ZOCOR consistently and significantly decreased total plasma cholesterol (TOTAL-C), LDL cholesterol (LDL-C), total cholesterol/HDL cholesterol (TOTAL-C/HDL-C) ratio, and LDL cholesterol/HDL cholesterol (LDL-C/HDL-C) ratio. ZOCOR also modestly decreased triglycerides (TRIG) and produced increases of variable magnitude in HDL cholesterol (HDL-C).

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

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

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

ZOCOR was compared to cholestyramine, probucol, or gemfibrozil, respectively, in double-blind parallel studies involving 1102 patients. All studies were performed in patients who were at moderate to high risk of coronary events based on serum cholesterol levels. At all dosage levels tested, ZOCOR produced a significantly greater reduction of total plasma cholesterol, LDL cholesterol, VLDL cholesterol, triglycerides, and total cholesterol/HDL cholesterol ratio when compared to cholestyramine or probucol. The increase in HDL seen with ZOCOR was not significantly greater than the increase seen with cholestyramine but was significantly different from the decrease seen with probucol (see Tables II and III).

TABLE II
ZOCOR vs. Cholestyramine
(Percent Change from Baseline After 12 Weeks)

TREATMENT	N	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	VLDL-C (median)	TRIG. (mean)
ZOCOR								
20 mg q.p.m.	84	–27	–32	+10	–36	–31	–8	–13
40 mg q.p.m.	82	–33	–41	+10	–45	–38	–28	–21
Cholestyramine 4-24 g/day**	85	–15	–21	+8	–25	–19	+7	+15

** maximum tolerated dose (mean dose taken, 18 g/day)

TABLE III
ZOCOR vs. Probucol
(Percent Change from Baseline After 12 Weeks)

TREATMENT	N	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	VLDL-C (median)	TRIG. (mean)
ZOCOR								
20 mg q.p.m.	82	–27	–34	+10	–39	–34	–18	–17
40 mg q.p.m.	80	–30	–40	+13	–45	–37	–14	–19
Probucol								
500 mg b.i.d.	81	–13	–8	–27	+31	+25	+11	–0.4

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

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

INDICATIONS AND USAGE

Therapy with lipid-altering agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. ZOCOR is indicated as an adjunct to diet for the reduction of elevated total and LDL cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb), when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacological measures alone has been inadequate.

Prior to initiating therapy with simvastatin, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure TOTAL-C, HDL-C, and triglycerides (TG). For patients with TG less than 400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation:

LDL-C = total cholesterol – [0.20 x (triglycerides) + HDL-C]

For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In many hypertriglyceridemic patients, LDL-C may be low or normal despite elevated TOTAL-C. In such cases, ZOCOR is not indicated.

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

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LDL-C = Total cholesterol – [0.20 x (triglycerides) + HDL-C]

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

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

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

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

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

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the TOTAL-C be used to monitor therapy.

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

***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	TG	T→C
V (rare)	chylomicrons, VLDL	TG	T→C

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

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The effect of simvastatin induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity or mortality has not been established.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as ZOCOR to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, ZOCOR may cause fetal harm when administered to a pregnant woman. Therefore, simvastatin is contraindicated during pregnancy and in nursing mothers. **Simvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, simvastatin should be discontinued and the patient should be apprised of the potential hazard to the fetus.**

WARNINGS

Liver Dysfunction

Persistent increases (to more than 3 times the upper limit of normal) in serum transaminases have occurred in 1% of patients who received simvastatin in clinical trials. When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pre-treatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically thereafter (e.g., semiannually). Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist, withdrawal of therapy with ZOCOR is recommended.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of simvastatin.

As with other lipid-lowering agents, moderate (less than three times the upper limit of normal) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and did not require interruption of treatment.

Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with simvastatin and other drugs in this class. The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibrates, niacin or erythromycin, and the daily dosage should not exceed 10 mg/day (see DOSAGE AND ADMINISTRATION).

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

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

PRECAUTIONS

General

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

Simvastatin may cause elevation of creatine phosphokinase and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with simvastatin.

Homozygous Familial Hypercholesterolemia

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

Information for Patients

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

Drug Interactions

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

Antipyrine: Because simvastatin had no effect on the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

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

transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and did not require interruption of treatment.

Skeletal Muscle

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

Muscle weakness accompanied by marked elevation of creatine phosphokinase was observed in a renal transplant patient on cyclosporine and simvastatin following the initiation of therapy with the systemic antifungal agent itraconazole. Rhabdomyolysis with renal failure has been reported in a renal transplant patient receiving cyclosporine and another HMG-CoA reductase inhibitor shortly after a dose increase in systemic itraconazole. The HMG-CoA reductase inhibitors and the azole derivative antifungal agents inhibit cholesterol biosynthesis at different points in the biosynthetic pathway. In patients receiving cyclosporine, simvastatin should be temporarily discontinued if systemic azole derivative antifungal therapy is required; patients not taking cyclosporine should be carefully monitored if systemic azole derivative antifungal therapy is required.

Physicians contemplating combined therapy with simvastatin and lipid-lowering doses of nicotinic acid, or with immunosuppressive drugs, should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Because of an apparent relationship between increased plasma levels of active metabolites derived from other HMG-CoA reductase inhibitors and myopathy, in patients taking [illegible] concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 ng/mL) in digoxin concentrations in plasma (as measured by a radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when simvastatin is initiated.

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

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

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. However, clinical studies have shown that simvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve, and does not reduce basal plasma testosterone concentration (see CLINICAL PHARMACOLOGY, *Clinical Studies*). Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG; the effect of simvastatin on HCG-stimulated testosterone secretion has not been studied. Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown. Patients treated with simvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g.,

ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity

Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 44 times higher than the mean drug level in humans taking 40 mg/day.

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

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced plasma drug levels that were about 50 times higher than the mean drug levels in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 3, 15, and 33 times higher than the mean human plasma drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high dose females and mid- and high-dose males with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day. Although mice were given up to 500 times the human dose (HD) on a mg/kg/body weight basis, blood levels of HMG-CoA reductase inhibitory activity were only 3-33 times higher in mice than in humans given 40 mg of ZOCOR, resulted in 6 times (rat) or 4 times (rabbit) the human exposure based on mg/m² surface area. However, in studies with another structurally related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took another HMG-CoA reductase inhibitor with dextroamphetamine sulfate during the first trimester of pregnancy. Simvastatin should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking simvastatin, it should be discontinued and the patient advised again as to the potential 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).

Pediatric Use

Safety and effectiveness in children and adolescents have not been established. Because children and adolescents 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 children or adolescents with simvastatin is not recommended at this time.

ADVERSE REACTIONS

In the controlled clinical studies and their open extensions (2423 patients with mean duration of follow-up of approximately 18 months), 1.4% of patients were discontinued due to adverse experiences attributable to ZOCOR. Adverse reactions have usually been mild and transient. ZOCOR has been evaluated for serious adverse reactions in more than 21,000 patients and is generally well tolerated.

Clinical Adverse Experiences

Adverse experiences occurring at an incidence of 1 percent or greater in patients treated with ZOCOR, regardless of causality, in controlled clinical studies are shown in the table below:

	ZOCOR (N=1583) %	Placebo (N=157) %	Cholestyramine (N=179) %	Probucol (N=61) %
Body as a Whole				
Abdominal Pain	3.2	3.2	8.9	2.5
Asthenia	1.6	2.5	1.1	1.2

cantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day. Although mice were given up to 500 times the human dose (HD) on a mg/kg/body weight basis, blood levels of HMG-CoA reductase inhibitory activity were only 3-33 times higher in mice than in humans given 40 mg of ZOCOR.

In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed. Although mice were given up to 31 times the human dose on a mg/kg basis, plasma drug levels were only 2-4 times higher than humans given 40 mg simvastatin as measured by AUC.

In a two-year study in rats, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 45 times higher levels of simvastatin than humans given 40 mg simvastatin (as measured by AUC).

A second two-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other HMG-CoA reductase inhibitors. These treatment levels represented plasma drug levels (AUC) of approximately 35 and 75 times (males) and 110 and 120 times (females) the mean human plasma drug exposure after a 40 milligram daily dose.

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

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (15 times the maximum human exposure level, based on AUC, in patients receiving 40 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day (which produces exposure levels 44 times higher than those in humans taking 40 mg/day), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day (approximately 7 times the human exposure level, based on AUC, at 40 mg/day). The clinical significance of these findings is unclear.

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Simvastatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses up to 10 mg/kg daily. These doses

below.

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

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

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

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

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration), dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

Laboratory Tests

Marked persistent increases of serum transaminases have been noted (see WARNINGS, *Liver Dysfunction*). About 5% of patients had elevations of creatine phosphokinase (CPK) lev-

els of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CPK. Muscle pain or dysfunction usually was not reported (see WARNINGS, *Skeletal Muscle*).

Concomitant Therapy

In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine. The combined use of simvastatin with fibrates should generally be avoided (see WARNINGS, *Skeletal Muscle*).

OVERDOSAGE

Significant lethality was observed in mice after a single oral dose of 9 g/m². No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 g/m², respectively. No specific diagnostic signs were observed in rodents. At these doses the only signs seen in dogs were emesis and mucoid stools.

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

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

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving ZOCOR and should continue on this diet during treatment with ZOCOR (see NCEP Treatment Guidelines for details on dietary therapy).

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

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

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

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.

Concomitant Therapy

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

Dosage in Patients with Renal Insufficiency

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

HOW SUPPLIED

No. 3588 — Tablets ZOCOR 5 mg are buff, shield-shaped, film-coated tablets, coded MSD 726 on one side and ZOCOR on the other. They are supplied as follows:

NDC 0006-0726-61 unit of use bottles of 60 (6505-01-354-4549, 5 mg 60's)

NDC 0006-0726-54 unit of use bottles of 90 (6505-01-354-4548, 5 mg 90's)

NDC 0006-0726-28 unit dose packages of 100.

No. 3589 — Tablets ZOCOR 10 mg are peach, shield-shaped, film-coated tablets, coded MSD 735 on one side and ZOCOR on the other. They are supplied as follows:

NDC 0006-0735-61 unit of use bottles of 60 (6505-01-354-4545, 10 mg 60's)

NDC 0006-0735-54 unit of use bottles of 90 (6505-01-354-4544, 10 mg 90's)

NDC 0006-0735-28 unit dose packages of 100 (6505-01-354-4543, 10 mg individually sealed 100's)

NDC 0006-0735-82 bottles of 1000

NDC 0006-0735-87 bottles of 10,000

No. 3590 — Tablets ZOCOR 20 mg are tan, shield-shaped, film-coated tablets, coded MSD 740 on one side and ZOCOR on the other. They are supplied as follows:

NDC 0006-0740-61 unit of use bottles of 60 (6505-01-354-4547, 20 mg 60's)

NDC 0006-0740-82 bottles of 1000

NDC 0006-0740-87 bottles of 10,000

No. 3591 — Tablets ZOCOR 40 mg are brick-red, shield-shaped, film-coated tablets, coded MSD 749 on one side and ZOCOR on the other. They are supplied as follows:

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

Storage

Store between 5-30°C (41-86°F).

7825414
ZOCOR® (Simvastatin)

Dist. by:
MERCK & CO., INC., West Point, PA 19486, USA

Issued November 1994
Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-766/S014

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date MAY 15 1995

NDA No. 19-766

Merck Research Laboratories
P.O. Box 4, BLA-30
West Point, PA 19486-0004

Attention: Robert E. Silverman, M.D., Ph.D

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: ZOCOR

NDA Number: 19-766

Supplement Number: S-014

Date of Supplement: May 9, 1995

Date of Receipt: May 11, 1995

Unless we find the application not acceptable for filing, the filing date will be 60 days from the receipt date above.

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Attention: Document Control Room 14B-03
5600 Fishers Lane, HFD-510
Rockville, MD 20857

Sincerely yours,

FYI Supervisory Consumer Safety Officer
Division of Metabolism and Endocrine Drug Products
Center for Drug Evaluation and Research

SLR 014

NDA SUPPLEMENT ORIGINAL

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

Merck & Co., Inc.
BLA-30
West Point PA 19486
Fax 610 397 2335
Tel 610 397 2944
215 652 5000

These copies are OFFICIAL FDA COPIES not desk copies.

NDA NO. 19766 REF. NO. 014

NDA SUPPL FOR SLR

MERCK Research Laboratories

May 9, 1995

Noted by Clinic 5/18/95

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

6/1/95 Accepted

Noted 5/17/95

Noted EKP 5/22/95

CENTER FOR DRUG REC'D MAY 11 1995 HFD-510 EVALUATION AND RESEARCH

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 [illegible] 21 CFR 314.70(c), we submit, for your approval, 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 (#7825414) has been modified under PRECAUTIONS to strengthen and clarify the existing product label description of potential drug interactions between simvastatin and warfarin based upon results from the pilot phase of the Oxford Cholesterol Study. This supplemental application is organized as a series of attachments:

Attachment 1: Summary of Revisions and Annotated Package Circular
Attachment 2: Rationale for Label Change
Attachment 3: References
Attachment 4: Final Printed Labeling (15 copies)

With this letter, we submit 15 copies of the Final Printed package circular (#7825414), a Summary of Revisions and a draft annotated package circular.

The changes will become effective on June 1, 1995 and will apply to all packages of ZOCOR distributed from the company's manufacturing facilities at West Point, Pennsylvania. It should be noted that this FPL will supercede #7825412 (submitted May 8, 1995). The label revision #7825413 has been discarded due to technical errors discovered prior to release.

We consider the filing of this Supplemental New Drug Application to be a confidential matter, and request the Food and Drug Administration not to 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).

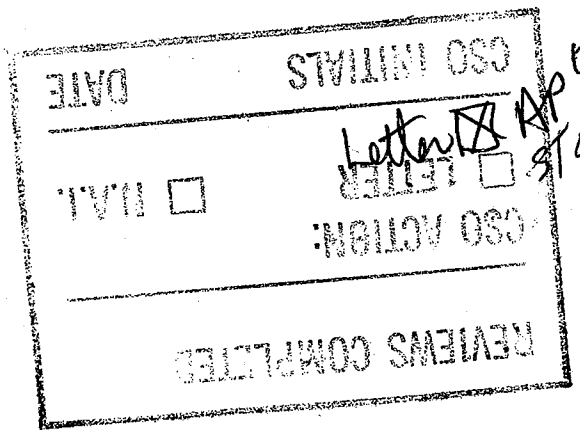
Sincerely yours,

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

mcs/q/ltr/171

Attachments
Circular No. 7825414
Certified #Z 747 795 432

Desk Copy: Mr. S. Trostle, HFD-511, Room 14B-04, Certified #Z 747 795 432



Letter AP 06/09/95
ST 06/15/95

USER FEE DATA ENTRY/VALIDATION FORM Ver.3(2/17/94)

NDA #19766 DOCUMENT ID/LETTER DATE SLR-01A / MAY 9, 1995

APPLICANT NAME MERCK

PRODUCT NAME ZOCOR (SIMVASTATIN)

FORM MUST BE COMPLETED ASAP

1. (YES) **User Fee Cover Sheet Validated?**

NOTE TO DOCUMENT ROOM:
PLEASE MAKE THE FOLLOWING CHANGES TO THE COMIS DATA ELEMENTS

2. YES (NO) **CLINICAL DATA?**
[Check YES if contains study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well controlled trials. "Clinical data do not include data used to modify the labelling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).]

REF **IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE *CROSS REFERENCED* IN ANOTHER SUBMISSION?**

3. YES (NO) **NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE** (OTHER THAN BUNDLING)? IF YES, list ALL NDA numbers, review divisions & indicate those for which application fees apply.

NDA #	DIVISION		
N_____	_____	FEE	NO FEE
N_____	_____	FEE	NO FEE

4. (YES) NO **BUNDLING POLICY APPLIED CORRECTLY? NO DATA ENTRY REQUIRED FOR ELEMENT**
[Check YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Check NO if application should be split into more than one application or submitted as an original instead of a supplement. IF NO, list resulting NDA numbers, and review divisions.]

NDA #	DIVISION	NDA #	DIVISION
N_____	_____	N_____	_____

5. P (S) **PRIORITY OR STANDARD?**

S. Smith 05/15/95

6. **CSO SIGNATURE/DATE** for **CSO CONCURRENCE SIGNATURE/DATE**

COPY DISTRIBUTION: ORIGINAL TO ARCHIVAL AFTER DATA ENTRY, ONE COPY BACK TO DIVISION FILE AND CDER, ASSOCIATE DIRECTOR FOR POLICY HFD-5

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

Form Approved: OMB No. *0910-0297*
Expiration Date: *November 30, 1996.*

USER FEE COVER SHEET

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Merck Research Laboratories
P.O. Box 4, BLA-30
West Point, PA 19486-0004

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

Merck Research Laboratories
P.O. Box 4, BLA-30
West Point, PA 19486-0004

ATTN: Bonnie J. Goldmann, M. D.
Executive Director
Regulatory Affairs

3. TELEPHONE NUMBER *(Include Area Code)* (610) 397-2383

4. PRODUCT NAME Zocor

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA? ☐ YES ☒ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

6. USER FEE I.D. NUMBER

7. LICENSE NUMBER/NDA NUMBER

8. 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 BEFORE 9/1/92

☐ AN INSULIN PRODUCT SUBMITTED UNDER 506

☐ THE APPLICATION IS SUBMITTED UNDER 505(b)(2) *(See reverse before checking box.)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

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

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

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

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION? ☐ YES ☐ NO *(See reverse if answered YES)*

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

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Bonnie J. Goldmann, M.D.	Executive Director Regulatory Affairs	May 9, 1995

FORM FDA 3397 (12/93)