

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-766/S008

Trade Name: Zocor Tablets

Generic Name: Simvastatin

Sponsor: Meck & Co, Inc.

Approval Date: April 19, 1995

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
19-766/S008

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter	
Labeling	X
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	X
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	X
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
19-766/S008

APPROVAL LETTER

APR 19 1995

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

Dear Dr. Silverman:

Please refer to your July 29, 1994, supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zocor (simvastatin) Tablets.

We acknowledge receipt of your amendments dated August 19 and 24, September 27, and October 27, 1994, and January 19, April 7 and 11, 1995. In addition, we refer to the telephone conversation between Bonnie Goldman, M.D. of Merck & Co., Inc. and Mr. Stephen Trostle of this Division in which Dr. Goldman agreed to correct  for the package insert.

This supplemental application provides for the revision of the package insert by adding the results of the Multicenter Anti-Atheroma Study (MAAS) to the CLINICAL PHARMACOLOGY section and a statement to the ADVERSE REACTIONS section regarding the incidence of adverse experiences in MAAS.

We have completed our review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the April 11, 1995, draft labeling. Accordingly, this supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the April 11, 1995, draft labeling.

Please submit fifteen copies of the FPL as soon as available. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "Final Printed Labeling" for approved supplemental NDA 19-766/S-008. Approval of this labeling by FDA is not required before it is used.

Should additional information relating to the safety or effectiveness of the drugs become available, revision of that labeling may be required.

Please incorporate all previous revisions as reflected in the most recently approved

package insert. To facilitate review of your submissions, please provide a highlighted or marked-up copy that shows the changes that are being made.

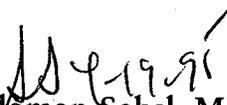
Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for these applications. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of the invoice.

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,


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/MRhee/EBarbehenn

HFD-510/STrostle/04/14/95/ft/stt/04/18/95 \N19766AP.008

Section affected:

ST 04/18/95
CLINICAL PHARMACOLOGY
ADVERSE REACTIONS

Concurrence:

EBarbehenn 04.14; MRhee, YChiu, AJordan, SAurecchia 04.17;
GTroendle, EGalliers 04.18.95

SUPPLEMENT APPROVAL (AP: NDA 19-766/S-008)

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-766/S008

LABELING

APPROVED 5-17-95 825415

ZOCOR® (Simvastatin)



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

TABLETS

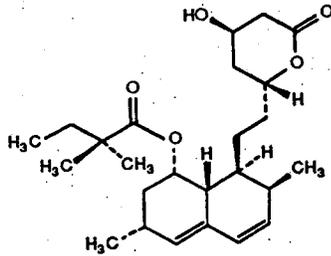
ZOCOR®

(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-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-(1 α ,3 α ,7 β ,8 β)(2S',4S')-8 α \beta]]. The empirical formula of simvastatin is C₂₅H₃₈O₅ and its molecular weight is 418.57. Its structural formula is:



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

Tablets ZOCOR for oral administration contain either 5 mg, 10 mg, 20 mg 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 experi-

Pharmacokinetics

Simvastatin is a lactone that is readily hydrolyzed *in vivo* to the corresponding β -hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the β -hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin.

Following an oral dose of ¹⁴C-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 ¹⁴C-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).

51

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-CPPPT), 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.

* Registered trademark of MERCK & CO., Inc.
COPYRIGHT © MERCK & CO., Inc., 1991
All rights reserved.

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).

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

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

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

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 dif-

ZOCOR® (Simvastatin)
7825415



ZOCOR® (Simvastatin)

ZOCOR® (Simvastatin)

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	-38	-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	-04

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

TABLETS
ZOCOR®
(SIMVASTATIN)

Circular Number 7825415



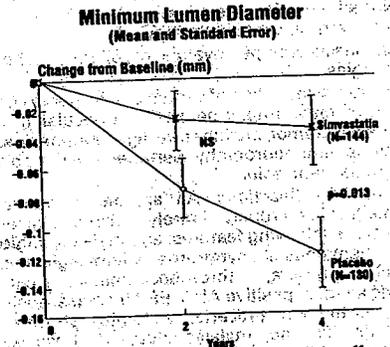
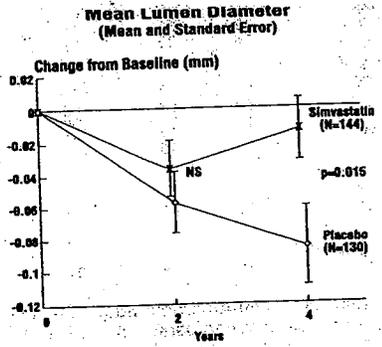
TABLETS
ZOCOR®
(SIMVASTATIN)

Circular Number 7825415



TABLETS
ZOCOR®
(SIMVASTATIN)

Circular Number 7825415
NDA 121-106-01 JUNE 1991



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



TABLETS
ZOCOR®
(SIMVASTATIN)

Circular Number 7825415



TABLETS
ZOCOR®
(SIMVASTATIN)

7825415



7825415

TABLETS
ZOCOR®
(SIMVASTATIN)

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:

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

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 many hypertriglyceridemic patients, LDL-C may be low or normal despite elevated TOTAL-C. In such cases, ZOCOR is not indicated.

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

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

Definite Atherosclerotic Disease†	Two or More Other Risk Factors†	LDL Cholesterol mg/dL (mmol/L)	
		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 atherosclerotic carotid artery disease).

ZOCOR® (Simvastatin)

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

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

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

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

Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been associated with simvastatin therapy. Rhabdomyolysis has also been associated with other HMG-CoA reductase inhibitors when they were administered alone or concomitantly with 1) immunosuppressive therapy, including cyclosporine in cardiac transplant patients; 2) gemfibrozil or lipid-lowering doses (≥1 g/day) of nicotinic acid in non-transplant patients; or 3) erythromycin in seriously ill patients. Some of the patients who had rhabdomyolysis in association with the reductase inhibitors had pre-existing renal insufficiency, usually as a consequence of long-standing diabetes. In most subjects who have had an unsatisfactory lipid response to either simvastatin or gemfibrozil

YES	YES OR NO	(≤4.7) ≥130 (≥3.4)	(≤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).

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,

*****Classification of Hyperlipoproteinemias**

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



ously 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 cyclosporine, the daily dosage should not exceed 10 mg/day (see DOSAGE AND ADMINISTRATION).

Simvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predispos-

ZOCOR® (Simvastatin)
 ing from the decrease seen with probucol (see Tables II and III)
 dom
 sum

ZOCOR® (Simvastatin)

ing 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, 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.

7825415

ZOCOR® (Simvastatin)

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

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

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

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

Endocrine Function

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

Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown. Patients treated with simvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase

inhibitor is used 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

ZOCOR® (Simvastatin)

formation at 10 mg/kg/day, (approximately 7 times the human exposure level, based on AUC, at 40 mg/day). The clinical significance of these findings is unclear.

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Simvastatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses up to 10 mg/kg daily. These doses resulted in 6 times (rat) or 4 times (rabbit) the human exposure based on mg/m² surface area. However, in studies with another structurally-related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took another HMG-CoA reductase inhibitor with dextroamphetamine sulfate during the first trimester of pregnancy. Simvastatin should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking simvastatin, it should be discontinued and the patient advised again as to the potential 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 pre-marketing controlled clinical studies and their open extensions (2423 patients with mean duration of follow-up of approximately 18 months), 1.4% of patients were discontinued due to adverse experiences attributable to ZOCOR. Adverse reactions have usually been mild and transient. ZOCOR has been evaluated for serious adverse reactions in more than 21,000 patients and is generally well-tolerated.

Clinical Adverse Experiences

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

	ZOCOR (N = 1533) %	Placebo (N = 157) %	Cholestyramine (N = 179) %	Probucol (N = 81) %
<i>Body as a Whole</i>				
Abdominal pain	3.2	3.2	8.9	2.5
Asthenia	1.6	2.5	1.1	1.2
<i>Gastrointestinal</i>				
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
<i>Nervous System/ Psychiatric</i>				
Headache	3.5	5.1	4.5	3.7
<i>Respiratory</i>				
Upper respiratory infection	2.1	1.9	3.4	6.2

In the Multicenter Anti-Atheroma Study, the incidence of adverse experiences was comparable in the simvastatin and placebo treatment groups over the four years of the study.

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

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

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

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, 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.

7825415
ZOCOR® (Simvastatin)

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

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

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

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

Laboratory Tests
Marked persistent increases of serum transaminases have been noted (see WARNINGS, *Liver Dysfunction*). About 5% of patients had elevations of creatine phosphokinase (CPK) levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CPK. Muscle pain or dysfunction usually was not reported (see WARNINGS, *Skeletal Muscle*).

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

OVERDOSAGE
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 overdose 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 overdose with ZOCOR can be recommended.

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

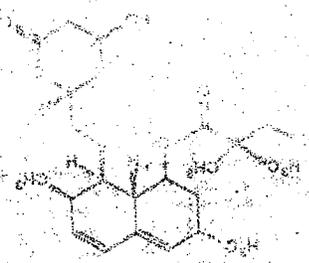
DOSEAGE AND ADMINISTRATION

ZOCOR® (Simvastatin)
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).

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

Issued November 1994
Printed in USA



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 (6505-01-354-4547; 5 mg 100's)

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)

[Faint, illegible text, likely bleed-through from the reverse side of the page.]

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-766/S008

MEDICAL REVIEW(S)

ORIGINAL

MAR 15 1995

NDA NO: 19-766/S-008

DRUG: ZOCOR® (simvastatin)

SPONSOR: Merck

DATE OF SUBMISSION: July 29, 1994

DATE OF AMENDMENT: September 28, 1994

REVIEW OF N.D.A.
LABELING SUPPLEMENT

This Supplement, as amended, provides for a description of efficacy results from the Multicenter Anti-Atheroma Study (MAAS) in text and graphical form in the CLINICAL PHARMACOLOGY, Clinical Studies section of the ZOCOR® (simvastatin) package insert. An additional statement in the ADVERSE REACTIONS section regarding the incidence of adverse experiences in MAAS is also requested.

I. Investigators

The trial was conducted at total of eleven (11) centers in Germany, France, the Netherlands, Sweden, Belgium, and England.

II. Design

Placebo-controlled, double-blind, randomized, parallel trial in patients undergoing routine coronary angiography. The randomization was stratified for clinical center and for concomitant treatment with anti-platelet agents and/or anti-coagulants.

III. Primary Objective

Assess the impact of simvastatin monotherapy over a four (4) year treatment period on coronary atherosclerosis, as measured angiographically.

IV. Intervention

Eligible subjects were maintained on a lipid-lowering diet, according to the practice of the center and randomized to either simvastatin 20 milligrams daily or matching placebo.

V. Inclusion Criteria

▼ Coronary angiography performed according to the pre-defined standards within 60 days of randomization. Patients were included with at least two coronary artery segments visibly involved with atherosclerosis, but not totally occluded and not requiring angioplasty or bypass surgery. Patients who had coronary artery bypass surgery were excluded. Segments involved in previous angioplasty were not to be evaluated in this study.

- ▼ Men and women age 30 through 67 years.
- ▼ Mean plasma cholesterol values for the first two screening visits in the range of 212 to 308 mg/dL (5.5 to 8.0 mmol/L). Mean triglycerides were to be less than 354 mg/dL (4.0 mmol/L).

VI. Exclusion Criteria

- ▼ Myocardial infarction or unstable angina within six weeks of the baseline angiogram and angioplasty or major surgery within three months of the baseline angiogram.
- ▼ Previous coronary artery bypass surgery.
- ▼ Premenopausal women unless surgically sterilized and postmenopausal women with their last menstrual period within one year of study entry.
- ▼ Hypertension with a diastolic blood pressure >100 mm Hg despite treatment.
- ▼ Fasting blood sugar >120 mg/dL (6.7 mmol/L) or fasting venous plasma glucose >140 mg/dL (7.8 mmol/L) or diabetes requiring therapy other than diet.
- ▼ Secondary hypercholesterolemia due to hypothyroidism, nephrotic syndrome, or other causes.
- ▼ A recent history of hepatitis or elevations to more than 50% above the normal range in alkaline phosphatase, ASAT, ALAT, or total bilirubin.
- ▼ Renal insufficiency with serum creatinine >150 μ mol/L.
- ▼ Clinical congestive heart failure or an ejection fraction of <30%.
- ▼ Weight exceeding 1.5 times ideal weight according to the Metropolitan criteria.
- ▼ Patients with a disease (other than coronary atherosclerosis) with a high likelihood of causing severe disability or death during the trial period.
- ▼ Patients receiving investigational drugs or any of the following: (1) lipid-lowering drugs within six weeks of enrollment; (2) estrogens; or (3) steroids.
- ▼ Alcohol or drug abuse.
- ▼ Partial ileal bypass.
- ▼ Complete biliary obstruction or symptoms or history of cholelithiasis.
- ▼ Psychosocial, physical, or mental situations that made completion of the study unlikely.
- ▼ Any other condition that, in the opinion of the investigator, made the patient unsuitable for the study.

VII. Primary Endpoint Angiographic Variables

Two continuous outcome variables served as co-primary endpoint parameters: 1) mean per-patient change from baseline in mean lumen diameter (in mm) of all lesions; and 2) mean per-patient change in minimum lumen diameter of the worst lesion in a segment with a threshold of $\geq 20\%$ stenosis at baseline or follow-

up. The worst lesion was defined as the one with the smallest absolute minimum lumen diameter at either baseline or follow-up.

VIII. Efficacy Results

The randomization was successful in generating comparable treatment groups with respect to sex, age distribution, race (the population was essentially all Caucasian) smoking history, use of antithrombotic therapy, proportions of patients with one or more secondary diagnoses, and distribution among functional cardiac classes (Canadian Heart Association). The treatment cohorts were also similar with regard to baseline cardiovascular history (angina pectoris, prior MI, prior PTCA, history of hypertension, mean systolic and diastolic blood pressures); angiographic characteristics, and lipid values.

Results for the each of the primary endpoints are summarized below (all-patients-treated analysis). The core laboratory staff performing the angiographic analysis was blinded to treatment assignment but not to film sequence.

MEAN LUMEN DIAMETER YEAR 2

	N/# segments	Pre-Mean	Post-Mean	CHANGE FROM BASELINE		
				Mean	S.D.	p-value
simvastatin	177/1365	2.83	2.79	-0.04	0.20	0.005
placebo	166/1304	2.82	2.76	-0.06	0.20	<0.001

At the year 2 timepoint, the mean value for the between-treatment group difference was 0.02 (p = 0.344) [95% CI: (-0.02, 0.06)].

MEAN LUMEN DIAMETER YEAR 4

	N/# segments	Pre-Mean	Post-Mean	CHANGE FROM BASELINE		
				Mean	S.D.	p-value
simvastatin	179/1365	2.85	2.82	-0.03	0.23	0.164
placebo	168/1309	2.82	2.74	-0.08	0.26	<0.001

At the year 4 timepoint, the mean value for the between-treatment group difference was 0.05 (p = 0.026) [95% CI: (0.01, 0.11)].

**MINIMUM LUMEN DIAMETER
YEAR 2**

	N/# segments	Pre-Mean	Post-Mean	CHANGE FROM BASELINE		
				Mean	S.D.	p-value
simvastatin	175/768	1.90	1.87	-0.03	0.23	0.09
placebo	165/748	1.91	1.82	-0.09	0.22	<0.00

At the year 2 timepoint, the mean value for the between-treatment group difference was 0.06 (p = 0.013) [95% CI: (0.01, 0.11)].

**MINIMUM LUMEN DIAMETER
YEAR 4**

	N/# segments	Pre-Mean	Post-Mean	CHANGE FROM BASELINE		
				Mean	S.D.	p-value
simvastatin	176/786	1.94	1.90	-0.04	0.25	0.02
placebo	167/782	1.91	1.79	-0.12	0.27	<0.00

At the year 4 timepoint, the mean value for the between-treatment group difference was 0.08 (p = 0.005) [95% CI: (0.02, 0.14)].

A number of non-primary endpoints, both angiographic and clinical, were also defined prospectively (see below). Selected results are summarized in Attachment I (all-patients-treated analyses).

▼ PROGRESSION:

This was defined as either 1) an increase of $\geq 15\%$ in percent diameter stenosis (averaged over matched projections) in a preexisting lesion (a preexisting lesion presents a percent diameter stenosis $\geq 20\%$); or 2) development of a new lesion-- a new lesion was characterized by a percent diameter stenosis $\geq 20\%$ at follow-up, an increase of $\geq 15\%$ in percent diameter stenosis and a baseline percent diameter stenosis $< 20\%$; or 3) progression to total occlusion.

▼ REGRESSION:

Regression was defined as either 1) a decrease of $\geq 15\%$ in percent diameter stenosis in a preexisting lesion (a preexisting lesion presents a percent diameter stenosis $\geq 20\%$) with follow-up percent diameter stenosis $\geq 20\%$; or

2) disappearance of a preexisting lesion--a disappearance is characterized by a percent diameter stenosis <20% at follow-up, a decrease of $\geq 15\%$ in percent diameter stenosis and a baseline percent diameter stenosis $\geq 20\%$; or 3) re-opening from total occlusion (not assessed by quantitative angiography but qualitatively).

Using these definitions, patients were classified into four categories:

- 1) Regressors: patients with at least one segment showing regression and no segments showing progression.
- 2) Progressors: patients with at least one segment showing progression and no segments showing regression.
- 3) Mixed: patients with segments showing progression and segments showing regression.
- 4) No Change: none of the above.

▼ OTHER:

Simvastatin and placebo were also compared based on other variables such as change from baseline in percent diameter stenosis and in mean and minimum lumen diameter according to the following lesion subgroups:

- 1) Lesions with $\geq 20\%$ diameter stenosis at baseline.
- 2) Lesions with $\geq 20\%$ and $< 50\%$ diameter stenosis at baseline.
- 3) Lesions with $\geq 50\%$ diameter stenosis at baseline.
- 4) Lesions with $\geq 20\%$ and $< 50\%$ and lesions with $\geq 50\%$ diameter stenosis at baseline or follow-up.
- 5) Lesions with total occlusion excluded.
- 6) Proximal and distal segments.
- 7) Right coronary, circumflex and left anterior descending artery.

Repeated measures analyses were also done for mean and minimum lumen diameters, and percent diameter stenosis in the subgroup of patients with both a two- and four-year angiogram (i.e., no data were carried forward from year 2 to year 4). Additionally, for these analyses, only coronary artery segments matching at baseline, year 2, and year 4 were used to calculate the per-patient endpoints.

Although the trial was neither designed nor powered to show differences between-treatment groups for clinical endpoints, the following were also summarized: 1) total mortality; 2) major coronary event (fatal myocardial infarction, nonfatal myocardial infarction, sudden death); 3) hospitalization for unstable angina; and 4) coronary revascularization procedures (PTCA and CABG). These clinical endpoints were assessed by a panel of three cardiologists, including the Chairman of the Steering Committee, without knowledge of the treatment assignment.

IX. Safety Data

Over the four-year treatment period, the treatment groups were similar with respect to the proportions of patients with adverse experiences, drug-related adverse events, and patients discontinued for adverse experiences. For serious adverse events, the proportion was higher in the placebo group (36% with simvastatin versus 45% with placebo, $p = 0.085$). Qualitatively, the profile of adverse clinical events in the simvastatin cohort was similar to that seen in other controlled trials and in open usage of simvastatin and other HMG CoA reductase inhibitors.

Overall there were a total of 15 deaths, 4 in the simvastatin group and eleven with placebo. All the simvastatin deaths were cardiac.

The numbers of patients with laboratory adverse experiences were similar between the two treatment groups (40.2% with simvastatin versus 45.5% with placebo), as were the numbers of patients with potentially drug-related events (24.0% with simvastatin versus 23.5% with placebo), and serious adverse events (1 or .05% in each group). Qualitatively, the profile of laboratory adverse events in the simvastatin cohort was again similar to that seen in other controlled trials and in open usage of simvastatin and other HMG CoA reductase inhibitors.

Liver function tests and CPK were analyzed specifically at months 1, 3, 6, 12, 18, 24, 30, 36, 42, and 48 with respect to the proportions of patients with changes outside predefined limits and to mean changes from baseline. For changes outside predefined limits, the placebo and simvastatin groups were generally similar, except for the following parameters and timepoints: for ALT, more elevations were seen in the placebo group at month 30 (8/181 versus 1/179 with simvastatin, $p = 0.037$). For alkaline phosphatase, larger proportions which achieved borderline significance were seen in the placebo group at months 24, 30, 42, and 48. For CPK at month 12, a higher proportion of subjects had elevations outside the pre-defined limit in the simvastatin treatment group (24/199 versus 11/197 with placebo, $p = 0.032$).

For ALT, the mean change from baseline in the simvastatin group ranged from 2.0 to 4.1 U/L and was significant ($p < 0.001$) at every month. Mean increases in the placebo group were significant at Months 24, 30, 36, 42, and 48. The mean change from baseline was significantly larger in the simvastatin group than in the placebo group at Month 1 ($p = 0.002$), at Month 3 ($p < 0.001$), at Month 6 ($p = 0.042$), at Month 12 ($p = 0.013$) and at Month 18 ($p = 0.009$). For AST, mean changes were significant ($p < 0.001$) in the simvastatin group at every month, ranging from 1.4 to 2.6 U/L. In the placebo group, mean significant increases were observed at Months 6, 12, 18, 24, 30, and 48. The mean

increase in the simvastatin group was significantly larger than the mean increase in the placebo group at Months 1 and 3 ($p < 0.001$), at Month 6 ($p = 0.003$), at Month 12 ($p = 0.026$), at Month 18 ($p = 0.035$), and at Month 24 ($p = 0.046$). For alkaline phosphatase, mean significant reductions were observed in the simvastatin group at Months 24, 30, 36, 42, and 48 while no significant changes were detected in the placebo group. The treatment groups were generally similar with respect to the mean change from baseline in alkaline phosphatase. At Month 48, the mean change from baseline was smaller in the simvastatin group than in the placebo group ($p = 0.037$). Mean increases in CPK were significant at every month in the simvastatin group and significant in the placebo group at every month except Months 1 and 3. At every visit, the treatment groups were similar with respect to the mean change from baseline in CPK. For total bilirubin, mean changes from baseline were small and generally not significant. At Months 36, 42, and 48 there was a mean significant increase in the simvastatin group of 0.8, 0.6 and 0.6 $\mu\text{mol/L}$, respectively. At each month the treatment groups were similar with respect to the mean change from baseline in total bilirubin.

Categorical analyses were also done for elevations in liver function tests greater than three times upper normal limits and for CPK values greater than ten times upper normal limits. These are summarized below:

PARAMETER	SINGLE ELEVATION				CONSECUTIVE ELEVATIONS			
	Simvastatin		Placebo		Simvastatin		Placebo	
	N	%	N	%	N	%	N	%
Total Bilirubin	0		0		0		0	
AST	1	0.5	2	1.0	0		0	
ALT	1	0.5	3	1.5	0		1	1.5
Alkaline Phosphatase	0		2	1.0	0		0	
CPK	0		0		0		0	

PROPOSED LABELING CHANGES: See attached.

COMMENTS: (see also Ms. Mele's Statistical Review)

The "pre-marketing" qualifier and the new statement regarding the adverse experience profile in "MAAS" proposed for the ADVERSE REACTIONS section are acceptable.

Regarding the proposed description of "MAAS" in the CLINICAL PHARMACOLOGY, Clinical Studies section:

more appropriate to state that results were statistically significant and report the magnitude of the treatment effect(s).

▼ The statement
should be deleted.

▼ In addition to the principal efficacy findings now cited in the labeling proposal, results for "progression" and "regression,"

consistency with the descriptions of the "CCAIT," "MARS," and "FATS" trials in the currently approved lovastatin package insert.

▼
were not statistically compared with respect to baseline factors of prognostic importance. The results for change from baseline mean and minimum lumen diameters were consistent with the all-patients-treated analyses of these variables, however, so I would favor permitting inclusion of these data as they are depicted graphically in the proposal.

RECOMMENDATION:

I would suggest the following for the CLINICAL PHARMACOLOGY, Clinical Studies section of the package insert:

In the Multicenter Anti-Atheroma Study, the effect of therapy with simvastatin on atherosclerosis was assessed by quantitative coronary angiography in hypercholesterolemic men and women with coronary heart disease. In this randomized, double-blind, controlled trial, patients with a mean baseline total cholesterol value of 245 mg/dL (6.4 mmol/L) and a mean baseline LDL value of 170 mg/dL (4.4 mmol/L) were treated with conventional measures and with simvastatin 20 mg/d or placebo. Angiograms were evaluated at baseline, two and four years. A total of 347 patients had a baseline angiogram and at least one follow-up angiogram.

The co-primary endpoints of the trial were mean change per-patient in minimum and mean lumen diameters, indicating

focal and diffuse disease, respectively.

simvastatin significantly slowed the progression of lesions as measured in the final angiogram by both these parameters (mean changes in minimum lumen diameter: -0.04 mm with simvastatin vs -0.12 mm with placebo; mean changes in mean lumen diameter: -0.03 mm with simvastatin vs -0.08 mm with placebo), as well as by change from baseline in percent diameter stenosis (0.9% simvastatin vs 3.6% placebo). After four years, the groups also differed significantly in the proportions of patients categorized with disease progression (23% simvastatin vs 33% placebo) and disease regression (18% simvastatin vs 12% placebo). In addition, simvastatin significantly decreased the proportions of patients with new lesions (13% simvastatin vs 24% placebo) and with new total occlusions (5% vs 11%). The mean change per-patient in mean and minimum lumen diameters calculated by comparing angiograms in the subset of 274 patients who had matched angiographic projections at baseline, two and four years is presented below.

(graph)

(graph)

Steven Aurecchia
Steven Aurecchia, M.D.

3/8/95
Alone Troendle
3-15-95

cc: NDA Arch 19-766
HFD-510
HFD-510/SAurecchia/GTroendle/STrostle
HFD-713/JMele

Robert
4/13/95

\\...\\SMVASTAT\\MAAS-008.REV

APPENDIX I

CATEGORICAL ANALYSES

YEAR 2	SIMVASTATIN		PLACEBO		p-VALUE*
	N	%	N	%	
Progression	31	17	44	27	0.050
Stable or Mixed	109	62	107	64	0.580
Regression	37	21	15	9	0.002
TOTAL	177		166		
*For between treatment group comparison					
YEAR 4	SIMVASTATIN		PLACEBO		p-VALUE*
	N	%	N	%	
Progression	42	23	55	33	0.057
Stable or Mixed	104	58	93	55	0.610
Regression	33	—	20	12	0.102
TOTAL	179		168		
*For between treatment group comparison					

NEW LESIONS/NEW OCCLUSIONS

YEAR 2	SIMVASTATIN		PLACEBO		p-VALUE*
	N	%	N	%	
New Lesions	16	9.0	31	18.7	0.012
New Occlusions	6	3.4	11	6.6	0.215
*For between treatment group comparison					
YEAR 4	SIMVASTATIN		PLACEBO		p-VALUE*
	N	%	N	%	
New Lesions	24	13.4	41	24.4	0.009
New Occlusions	8	4.5	18	10.7	0.040
*For between treatment group comparison					

PERCENT DIAMETER STENOSIS
(All Qualifying Segments)

YEAR 2	N/# segments	Pre-Mean	Post-Mean	CHANGE FROM BASELINE		
				Mean	S.D.	p-value
simvastatin	175/768	31.5	31.0	-0.5	7.2	0.348
placebo	165/748	30.5	32.8	2.3	6.1	<0.001

At the year 2 timepoint, the mean value for the between-treatment group difference was -2.8 (p = <0.001) [95% CI: (-4.3, -1.4)].

YEAR 4	N/# segments	Pre-Mean	Post-Mean	CHANGE FROM BASELINE		
				Mean	S.D.	p-value
simvastatin	176/786	30.7	31.6	0.9	7.9	0.116
placebo	167/782	30.6	34.2	3.6	9.0	<0.001

At the year 4 timepoint, the mean value for the between-treatment group difference was -2.8 (p = 0.003) [95% CI: (-4.6, -0.9)].

CHANGE IN MEAN LUMEN DIAMETER
(Segments with %S ≥20% at Baseline)

YEAR 4	N/# segments	Pre-Mean	Post-Mean	CHANGE FROM BASELINE		
				Mean	S.D.	p-value
simvastatin	173/690	2.57	2.54	-0.03	0.28	0.148
placebo	164/653	2.52	2.41	-0.11	0.37	<0.001

At the year 4 timepoint, the mean value for the between-treatment group difference was 0.08 (p = 0.024) [95% CI: (0.01, 0.15)].

CHANGE IN MINIMUM LUMEN DIAMETER
(Segments with %S ≥20% at Baseline)

YEAR 4	N/# segments	Pre-Mean	Post-Mean	CHANGE FROM BASELINE		
				Mean	S.D.	p-value
simvastatin	173/690	1.85	1.87	0.02	0.25	0.333
placebo	164/653	1.80	1.73	-0.07	0.28	0.003

At the year 4 timepoint, the mean value for the between-treatment group difference was 0.08 (p = 0.004) [95% CI: (0.03, 0.14)].

CHANGE IN MEAN LUMEN DIAMETER
(All Segments Analyzed at Baseline, Year 2, and Year 4)

	N/# Segments	Baseline Mean (S.D.)	Year 2 Mean (S.D.)	Year 4 Mean (S.D.)	CHANGE FROM BASELINE	
					Year 2 (S.D.)	Year 4 (S.D.)
simvastatin	144/1063	2.84 (0.37)	2.80 (0.38)	2.82 (0.41)	-0.04 (0.21)	-0.02 (0.23)
placebo	130/973	2.84 (0.40)	2.78 (0.42)	2.75 (0.45)	-0.06 (0.21)	-0.09 (0.27)

p-Value for Treatment Effect at Year 2 = 0.318
p-Value for Treatment Effect at Year 4 = 0.015

CHANGE IN MINIMUM LUMEN DIAMETER
(All Segments Analyzed at Baseline, Year 2, and Year 4)

	N/# Segments	Baseline Mean (S.D.)	Year 2 Mean (S.D.)	Year 4 Mean (S.D.)	CHANGE FROM BASELINE	
					Year 2 (S.D.)	Year 4 (S.D.)
simvastatin	144/681	1.95 (0.36)	1.92 (0.36)	1.91 (0.36)	-0.03 (0.24)	-0.04 (0.27)
placebo	130/619	1.94 (0.37)	1.87 (0.42)	1.82 (0.45)	-0.07 (0.22)	-0.12 (0.29)

p-Value for Treatment Effect at Year 2 = 0.107
p-Value for Treatment Effect at Year 4 = 0.013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
19-766/S008

STATISTICAL REVIEW(S)

MAR 2 1995

STATISTICAL REVIEW AND EVALUATION

NDA #: 19 766/SLR-008

Applicant: Merck Research Laboratories

ORIGINAL

Name of Drug: Zocor (simvastatin)

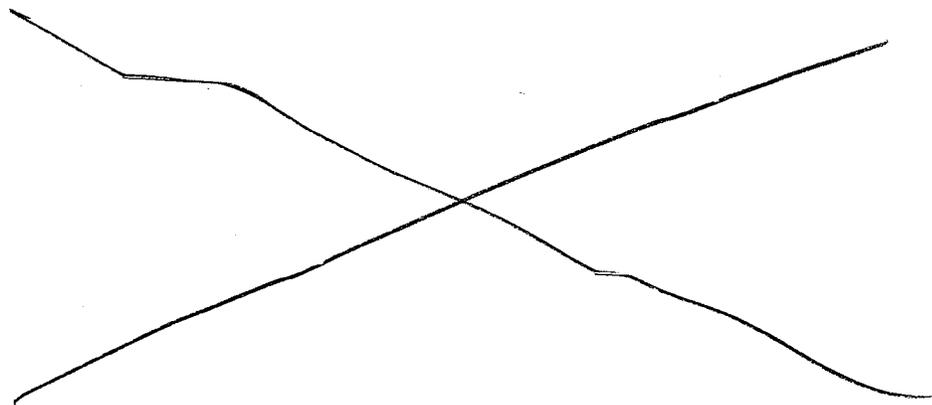
Indication: Adjunct to diet for the reduction of total and LDL cholesterol levels

Documents Reviewed: Volumes 1 and 9 through 12 dated 7/29/94

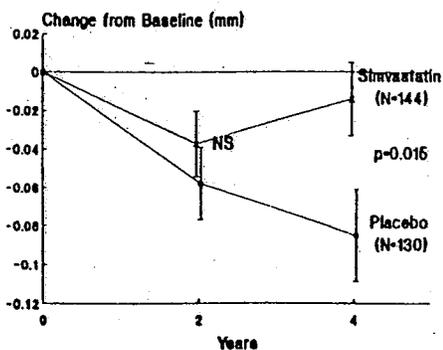
Medical Input: Dr. Steven Aurecchia (HFD 510) was consulted during the review process.

Introduction

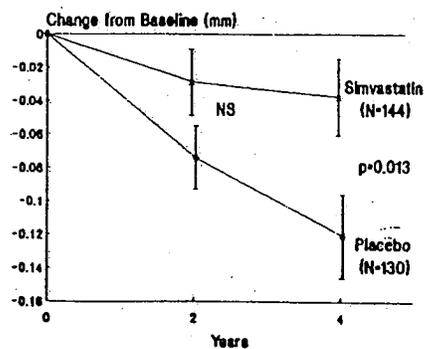
The sponsor has submitted the results of the Multicenter Anti Atheroma Study (MAAS) to support changes to the Clinical Pharmacology section of the label for Zocor. The proposed labeling is as follows:



Mean Lumen Diameter
(Mean and Standard Error)



Minimum Lumen Diameter
(Mean and Standard Error)



Trial Design

The MAAS trial was a multicenter, randomized, double-blind, parallel trial designed to evaluate the progression of atherosclerosis in the coronary arteries of patients treated with simvastatin compared to placebo-treated patients. Men and women aged 30 to 67 years with at least two diseased coronary segments visible by angiography and with mean plasma cholesterol of 212 to 308 mg/dL (5.5 to 8 mmol/L) and mean triglycerides less than 354 mg/dL (4 mmol/L) were eligible for this trial. Patients were randomized, stratified on antithrombotic therapy (yes/no) and center, to simvastatin (20 mg per day) or placebo. Responses were measured by quantitative coronary angiography.

The study was originally planned as a two-year study with 2 angiograms; one at baseline (within 1 month of randomization) and one after 2 years on treatment. Before the completion of the 2 years, the data safety monitoring board (DSMB)¹ modified the protocol to extend the length of the trial an additional two years and to add an interim analysis plan to be performed when all patients had completed 2 years of therapy and had a second angiogram (see Table 1 below).

Table 1. Order of events leading up to the interim analysis as ascertained by this reviewer based on sponsor's submission and published manuscripts.

Date of Event	Event
8/16/90	Protocol modified to include extension of the trial to 4 years
6/13/91	DSMB met to discuss endpoints and stopping rules
1/16/92	Endpoints and stopping rules were defined in protocol revision
2/92	Interim analysis performed

The interim analysis (Year 2) stopping rule based on 2 co-primary endpoints was as follows:

- 1) A combined p-value for the 2 co-primary endpoints $\leq .01$ and at least one primary endpoint p-value $\leq .05$
- or
- 2) a p-value for at least one primary endpoint $\leq .01$.

The rule at the final analysis (Year 4) for establishing efficacy was as follows:

- 1) A combined p-value for the 2 co-primary endpoints $\leq .02$ and at least one primary endpoint p-value $\leq .05$
- or
- 2) a p-value for at least one primary endpoint $\leq .02$.

By simulations, the sponsor established that an overall alpha level of .05 was not

¹ The DSMB was comprised of 3 committees; Steering Committee, Data Monitoring and Ethical Committee and the Interim Evaluation Committee. Only the members of the third committee saw the results of the 2-year interim analysis and made recommendations to the Steering Committee without revealing the efficacy results.

exceeded using the above rules.

The DSMB decided to continue the trial an additional 2 years based on negative interim analysis results, therefore patients continuing on study had a third angiogram at Year 4.

The 2 co-primary endpoints were mean lumen diameter (averaged over all segments) and minimum lumen diameter (averaged over the worst lesions of all segments $\geq 20\%S$ at baseline or endpoint). Progression/regression measured categorically was considered a secondary endpoint. Tertiary endpoints were based on subgroups (defined by lesion size and placement) of the primary variables and of percent diameter stenosis.

Results

Patient Disposition and Demographics

A total of 404 patients (204 simvastatin and 200 placebo) were randomized to treatment at 11 European centers. Patients were predominantly male (89%) and Caucasian (98%). Seventy percent of the patients were under 60, 23% were 60 to 64 and 7% were 65 and older. About one quarter of the patients were current smokers; 86% had a history of smoking. Two percent of the patients had diabetes.

The major reason for discontinuation from the study in both treatment groups was an unwillingness to continue (a total of 14% in each group, Table 2). About 80% of the patients completed the first 2 years of the study and about 70% completed the full 4 years. Note that some patients had angiographic data even though they dropped out during the trial.

Table 2. Patient Disposition

	Simvastatin	Placebo
Randomized	204	200
Dropouts during Year 1 and Year 2		
Clinical AE	5	12
Unwilling	15	17
Insufficient baseline	10	11
Other	5	5
Year 2 Completers	169 (83%)	155 (78%)
Number of Patients with Year 2 Angiographic Data	177 (87%)	166 (83%)
Dropouts during Year 3 and Year 4		
Clinical AE	4	4
Unwilling	13	10
Other	7	8
Year 4 Completers	145 (71%)	133 (67%)
Number of Patients with Year 4 Angiographic Data	146 (72%)	132 (66%)
Number of Patients Included in LOCF Analysis ¹	179 (88%)	168 (84%)

¹ The number of patients in the last-observation-carried-forward (LOCF) analysis is larger than the number with Year 2 data because 4 patients were missing Year 2 data but had Year 4 data.

The mean dose of simvastatin for the 179 patients included in the LOCF analysis was 19.3 mg (range of 0.7 mg to 20 mg).

The treatment groups were comparable at baseline with regard to cardiovascular parameters (e.g., MI, angina, BP) and lipid values (see Table 3 below). About one-third of the patients in each group were on antithrombotic therapy.

Table 3. Lipid Values at Baseline

Lipids (mmol/L)	Simvastatin Mean (SD) [Range]	Placebo Mean (SD) [Range]
LDL C	4.4 (0.7) [2.8, 6.2]	4.5 (0.8) [2.4, 6.6]
HDL C	1.1 (0.3) [0.7, 2.4]	1.1 (0.3) [0.6, 2.2]
Total Cholesterol	6.4 (0.7) [5.0, 8.2]	6.4 (0.8) [4.0, 8.8]
Total Triglycerides	1.9 (0.9) [0.6, 5.6]	1.8 (0.8) [0.6, 5.0]

Reviewer's Comments

In the proposed label (second sentence), the sponsor presents the total cholesterol and LDL for the patient sample _____ respectively. The total cholesterol of _____

Note from the table above that 4 to 8.8 was the observed range for cholesterol. The sponsor should modify the label _____

Sponsor's Results

The sponsor's primary analysis was an "all patients treated" analysis where all randomized patients with a baseline and followup angiogram were included in the analysis. For patients missing data at Year 4, results from an earlier angiogram were used. (This analysis is a last observation carried forward analysis.) The sponsor also performed a per protocol analysis where protocol violators (such as, patients with data outside predefined day ranges) were excluded.

The sponsor performed the following analyses on the primary efficacy variables:

1. Analysis of variance with center, treatment and the interaction in the model (interaction term was excluded if no qualitative interaction was observed)
2. Nonparametric rank analysis
3. Analysis of variance with center, treatment and stratum (use of antithrombotic therapy) in the model

4. Correlation analyses between lipids and primary efficacy variables
5. Correlation analyses between risk factors and primary efficacy variables
6. Subgroup analyses based on gender, age, baseline lipid values and antithrombotic therapy.
7. Repeated measures analysis with center, treatment, subject (random effect), time, time by treatment interaction and time by center interaction in the mixed model.
8. Global test of 2 co-primary endpoints.¹

For the secondary categorical endpoints, Fisher's Exact test or the Wilcoxon Rank-Sum test were used. For the tertiary endpoints, similar analyses (dependent on the type of variable) were performed.

Appears This Way
On Original

¹Test described by Pocock, Geller and Tsiatis in *Biometrics* 43:487-498, 1987.

The sponsor's ANOVA results (the first analysis listed above) for the two primary efficacy variables (Table 4) show a statistically significant difference between simvastatin and placebo at Year 4 for both the "all patients" dataset (LOCF) and the "per-protocol" dataset; the means of both groups show disease progression based on mean and minimum lumen diameter with significantly larger changes (more progression) in the placebo group. The global test results support the separate endpoint results ($p = .055$ at Year 2 and $p = .007$ at Year 4).

Table 4. Sponsor's Results for the Primary Efficacy Variables

	Simvastatin Mean (SD)	Placebo Mean (SD)	Treatment Difference (95% CI)	P value
Mean Lumen Diameter				
# Segments ¹ Baseline	7.7 (1.3) 2.85 (0.38)	7.8 (1.5) 2.82 (0.41)		
Change at 2 years ² All patients	-0.04 (0.20) (n = 177)	-0.06 (0.20) (n = 166)	0.02 (-0.02, 0.06)	.34
Change at 4 years Per protocol	-0.02 (.23) (n = 136)	-0.08 (.27) (n = 122)	0.07 (0, 0.13)	.04
All patients (LOCF)	-0.03 (.23) (n = 179)	-0.08 (.20) (n = 168)	0.06 (0.01, 0.11)	.03
Minimum Lumen Diameter				
# Segments ³ Baseline	4.5 (1.7) 1.94 (0.38)	4.7 (1.8) 1.91 (0.39)		
Change at 2 years ² All patients	-0.03 (.23) (n = 175)	-0.09 (.22) (n = 165)	0.06 (0.01, 0.11)	.01
Change at 4 years Per protocol	-0.05 (.26) (n = 134)	-0.13 (.29) (n = 121)	0.08 (0.01, 0.15)	.03
All patients	-0.04 (.25) (n = 176)	-0.12 (.27) (n = 167)	0.08 (0.02, 0.14)	.005

The test for center by treatment interaction was significant for mean lumen diameter ($p = .01$) but not for minimum lumen diameter ($p = .77$). A test for qualitative interaction on the former measure was nonsignificant ($p > .10$) and according to the sponsor the results were

¹All diseased segments matched at baseline and endpoint.

²A decrease indicates disease progression.

³All segments with 20% stenosis at baseline or followup.

consistent across centers. (Results by center were not presented in the submission and were requested by this reviewer. Those results showed that, at Year 2, the placebo response was greater than the simvastatin response at 6 of the 11 centers while at Year 4 only one of those centers showed a reversal.)

The sponsor also performed a repeated measures analysis on all patients with data at Year 2 and Year 4. A total of 144 simvastatin patients and 130 placebo patients (68% of the randomized patients) were included in this analysis. The results for the primary efficacy variables and percent diameter stenosis revealed significant treatment by time interactions; therefore the sponsor presented the treatment effects for each year separately. The results by year were consistent with the sponsor's LOCF results.

Reviewer's Analyses and Comments

The sponsor presented the results of an LOCF analysis at Year 4. These results may be biased for or against drug dependent on the dropout pattern observed in each group. To determine the influence of dropouts we can compare the results for patients having data at Year 4 (observed cases) to the LOCF results.

Of the 347 patients used in the LOCF analysis, 69 patients (20%) had only Year 2 data (see the last 2 lines of Table 2 on page 3). This reviewer excluded those 69 patients, analyzing the observed cases data only. The results of this observed cases analysis of the primary efficacy variables are consistent with the sponsor's results (Table 8).

Table 8. Reviewer's Observed Cases Analysis of Primary Efficacy Variables

	Simvastatin Mean (SD)	Placebo Mean (SD)	p-value
Mean Lumen Diameter	(n = 146)	(n = 132)	
Baseline	2.8 (0.4)	2.8 (0.4)	
4-Year Change	-0.01 (0.23)	-0.08 (0.27)	.02
Minimum Lumen Diameter	(n = 144)	(n = 131)	
Baseline	1.9 (0.4)	1.9 (0.4)	
4-year Change	-0.05 (0.27)	-0.12 (0.29)	.02

**Appears This Way
On Original**

Progression was defined as an increase of at least 15%S in new or existing lesions or progression to total occlusion while regression was defined as a decrease of at least 15%S or disappearance of a pre-existing lesion or re-opening from total occlusion. The results for progression/regression (Table 5) show that the groups were significantly different after both 2 and 4 years for the all patients analysis.

Table 5. Sponsor's Results for Progression/Regression (Secondary Efficacy Variable)

	Simvastatin	Placebo	p-value
At 2 years All Patients	n = 177	n = 166	
Progression Only	31 (18%)	44 (27%)	.002
No Change/Mixed	109 (62%)	107 (64%)	
Regression Only	37 (21%)	15 (9%)	
At 4 years Per Protocol	n = 136	n = 122	
Progression Only	38 (28%)	44 (36%)	.11
No Change/Mixed	73 (54%)	62 (51%)	
Regression Only	25 (18%)	16 (13%)	
At 4 years All Patients	n = 179	n = 168	
Progression Only	42 (24%)	55 (33%)	.02
No Change/Mixed	104 (58%)	93 (55%)	
Regression Only	33 (18%)	20 (12%)	

Reviewer's Comments

These results are not as striking as the treatment differences presented in the lovastatin labeling describing the results for MARS and CCAIT (12% and 17%, respectively) which may explain why

The proposed labeling states the results

Note that the percentage of new lesions and new total occlusions is about double for the placebo patients compared to the simvastatin patients.

Table 6. Sponsor's Results for Secondary and Tertiary Efficacy Variables

	Simvastatin	Placebo	Treatment Difference (95% CI)	P value
New Lesions			not provided	
At 2 years All patients	16/177 (9%)	31/166 (19%)		.01
At 4 years Per protocol	19/136 (14%)	32/122 (26%)		.02
All patients	24/179 (13%)	41/168 (24%)		.01
New Total Occlusions			not provided	
At 2 years All patients	6/177 (3%)	11/166 (7%)		.22
At 4 years Per protocol	8/136 (6%)	15/122 (12%)		.08
All patients	8/179 (5%)	18/168 (11%)		.04
Percent Diameter Stenosis	Mean (SD)	Mean (SD)		
Mean # Segments Baseline	4.5 (1.7)	4.7 (1.8)		
	30.7 (6.4)	30.6 (6.8)		
Change at 2 years ¹ All patients	-0.5 (7.2) (n=175)	+2.3 (n=165)	-2.8 (-4.3, -1.4)	<.001
Change at 4 years Per protocol	+1.6 (8.0) (n=134)	+4.1 (9.8) (n=121)	-2.8 (-5.1, -0.6)	.01
All patients	+0.9 (7.9) (n=176)	+3.6 (9.0) (n=167)	-2.8 (-4.6, -0.9)	.003

The LDL, HDL and total cholesterol results showed significant beneficial changes for simvastatin compared to placebo with treatment differences significant at the .001 level at every measurement point from Month 1 to Month 48. Triglycerides significantly decreased ($p < .001$) in the simvastatin group for the first 18 months of the trial and then steadily increased on the average during the last 2 years of the study so that at Month 48 the

¹An increase indicates disease progression.

treatment difference was not significant (+ 2% change for simvastatin compared to + 7.7 % change for placebo, $p = .220$).

The sponsor performed a correlation analysis of lipid response with mean and minimum lumen diameter and found the measures to be significantly negatively correlated (except for HDL which was positively correlated with outcome, $r < +.2$). The Spearman rank correlations ranged from -.01 to -.14 for mean lumen diameter and from -.04 to -.22 for minimum lumen diameter. For all lipid measures, correlations were higher for minimum lumen diameter than for mean lumen diameter.

Reviewer's Comments

The magnitudes of the coefficients were small ($r < .2$) indicating a weak association between lipid changes and angiographic changes. The fact that the correlations are statistically significantly different from zero is a result of the large sample size not of the strength of association.

The sponsor presented descriptive statistics for subgroups based on gender, age (< 65 versus ≥ 65) and use of antithrombotic therapy (the stratifier at randomization). Tests for interaction were not significant for any of these subgroup variables. Since only 11% of the patients were female and only 7% were over 65, the sample sizes were too small to compare subgroups and so there were no notable subgroup differences. The results for the stratifier shown below suggest a more favorable response for patients using antithrombotic therapy at baseline.

Table 7. Angiographic Results by Use of Antithrombotic at Baseline

	Mean Treatment Difference	
	Yes (n=234)	No (n=113)
Mean Lumen Diameter	+0.07	+0.03
Minimum Lumen Diameter	+0.11	+0.02
Percent Stenosis	-3.1	-2.0

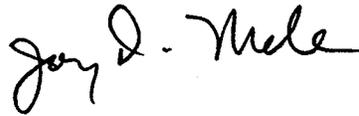
Reviewer's Overall Comments

1. Even though both men and women were included in the study, only 11% of the patients were women.
2. The observed range for total cholesterol at baseline was 4 to 8.8 mmol/L
3. Sentence #5 of the proposed labeling states

4

the observed treatment differences (as presented on page 636 of the MAAS publication¹) and merely state that the results for the primary efficacy variables were statistically significant even when accounting for multiple endpoints and an interim analysis.

5. The graphs proposed for the labeling represent a subset of the patients studied; the data is from 78% of the patients included in the Year 4 LOCF analysis and only 67% of all the patients randomized. Nevertheless, the graphs are similar to those for the LOCF data and therefore do not misrepresent the results of this trial. (See Attachment 1.)



Joy D. Mele, M.S.
Mathematical Statistician

Concur: Dr. Nevius *89m 2-28-95*

Dr. Dubey *6-3-1-95*

cc:

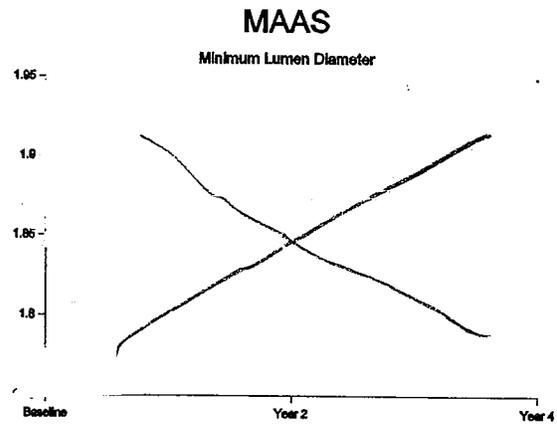
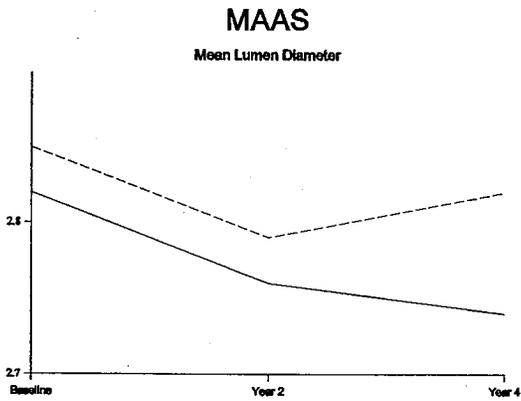
Orig. NDA 19-766
HFD 510
HFD 510/Drs. Aurrechia, Troendle, and Sobel
HFD 510/Mr. Trostle
HFD 713/Dr. Dubey [File: DRU 1.3.2]
HFD 713/Group 2 File
HFD 713/Ms. Mele
HFD 344/Dr. Lisook

Mele/x4 5478/SERB/WordPerfect Windows Zocor2.rev/February 15, 1995
This review consists of 11 pages plus one attachment.

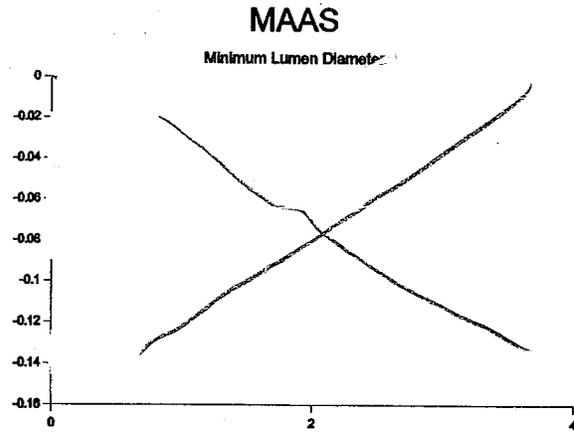
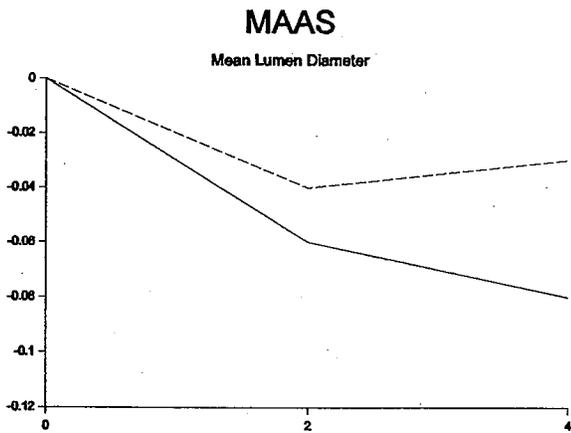
¹ The MAAS Investigators state on page 636 (in Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS). *The Lancet* 1994; 344: 633-638) "Simvastatin had a treatment effect of +0.06 mm on mean lumen diameter and of ~~0.06 mm~~ on minimum lumen diameter."

ATTACHMENT 1

1. Graphs of the LOCF results including baseline and Years 2 and 4.



2. Graphs of the LOCF change from baseline results at Years 2 and 4.



**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
19-766/S008

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

ORIGINAL

NDA 19-766/S-008

MAY 17 1995

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

Dear Dr. Silverman:

We acknowledge the receipt of your May 10, 1995, submission containing final printed labeling in response to our April 19, 1995, letter approving your supplemental new drug application for Zocor (simvastatin) Tablets.

We have reviewed the labeling that you have submitted in accordance with our April 19, 1995, letter, and we find it acceptable.

Sincerely yours,

STrostle 5-16-95
for

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

- cc: Orig NDA
- HFD-510
- DISTRICT OFFICE (w/labeling)
- HF-2/MEDWATCH (w/labeling)
- HFD-85 (w/labeling)
- HFD-240/(w/labeling)
- HFD-618/(w/labeling)
- HFD-735/DBarash/(w/labeling)
- HFD-510/SAurecchia/MRhee/EBarbehenn
- HFD-510/STrostle/05/15/95/ft/stt/05/15/95 \N19766AR.008

ST05/15/95

Concurrence: LPauls for EGalliers 05.15.95

ACKNOWLEDGE AND RETAIN (AR)

AUG 30 1994

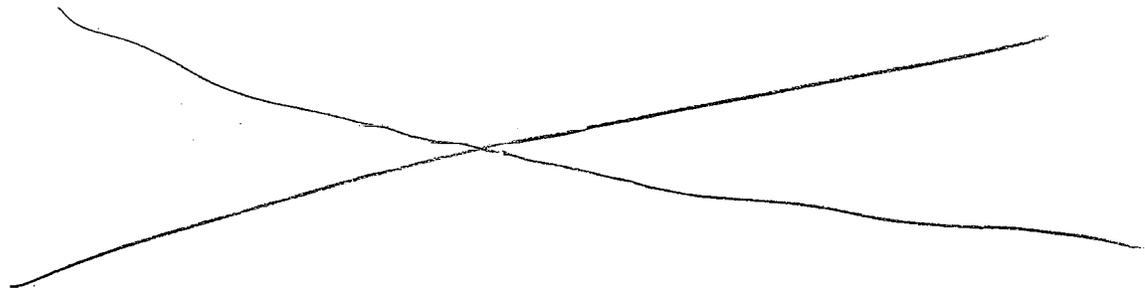
AUG 30 1994

NDA 19766/S-008
Simvastatin
Lipid altering

Merck
Received 7-29-94
Comments written 8-30-94

GROUP LEADER'S - Comments on NDA Supplement

ORIGINAL



There are two publications that include analysis of angiographic changes and their correlation with subsequent coronary events. A third publication (Brown, et al., New Engl J Med 1990, 323:1289-1298) includes data from the FATS trial on angiographic endpoints and on coronary events, each significantly improved by lipid therapy,

Buchwald, et al. (JAMA 1992, 268:1429-1433) described the POSCH trial, using partial ileal bypass to control lipids. 417 patients were randomly assigned to receive diet and 421 ileal bypass with mean followup of 9.7 years (7 to 14.8). Patients were stratified by changes in angiographic findings between baseline and 3 years. Seven categories were described, -3 (marked progression), -2, -1, -0, +0, +1, +2 (regression). No patients appear to have gotten a rating of +3 for "marked regression." For overall mortality linear trend, p = .01. For ACHD mortality or MI controls, linear trend p = .0001 and for surgery p = .04.

	-3	-2	-1	-0	+0	+1	+2
Overall mortality, control #	11	48	79	107	64	21	3
% with endpoint	9.1	12.5	11.4	11.2	7.8	9.5	0%
surgery #	7	33	62	120	107	25	8
% with endpoint	28.6	12.1	11.3	6.7	4.7	4.0	0%
total #	18	81	141	227	171	46	11
% with endpoint	16.7	12.3	11.3	8.8	5.8	6.5	0%
ACHD mort + MIs control	45.5	35.4	30.4	19.6	7.8	19.0	0%
(% with endpoint) drug	14.3	21.2	12.9	9.2	6.5	8.0	12.5

However, it is interesting to note the difference between the correlation in control and surgery patients, and information on total patients was not correlated for the outcome that includes non-fatal MIs. Certainly if there was progression (-0 to -3), the outcome was considerably worse than if there was no progression. Most of the patients with progression were in the

-0 category (227 patients vs 18 in the -3 category and 222 in the other two progression categories), and 228 patients had regression of any degree.

Waters, et al., (Circulation 1993, 87:1067-1075) described a study of nicardipine post infarction for effects on coronary events and angiographic lesion progression/regression. Nicardipine was determined to have no effect on advanced coronary atherosclerosis, so the drug and control groups were combined and analyzed for differences between progressors (n = 141) and nonprogressors (n = 194). Coronary angiography was done at baseline and two years, with further followup for a mean of 44 months (9 to 80). Progression was defined as $\geq 15\%$ increase in diameter stenosis. During the followup, cardiac deaths were (progressors vs nonprogressors) 16 vs 3 (RR 7.3, CI 2.2-24.7, $p < .001$), cardiac deaths or nonfatal MI were 25 vs 15 (RR 2.3, CI 1.3-4.2, $p = .009$), and any cardiac event 62 vs 50 (RR 1.7, CI 1.3-2.3, $p < .001$).

but they represent only a small portion of the angiographic studies that have been reported. What we lack on most of the studies is followup data on endpoints.

Hong, et al., reviewed 9 studies for the value of angiography in determining progression/regression. This review does not include any data on endpoints.

However, most of the angiography studies are on lipid-altering drugs.

Gloria Troendle/9-1-94

Gloria Troendle

cc: NDA Arch (NDA 19-766/S-008)

HFD-S10

HFD-S10/GTroendle/SAnnicchiè/PBarbieri/SNostle



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date **AUG 3 1994**

NDA No. 19-766

Merck Research Laboratories
Sumneytown Pike
West Point, PA 19486

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-008

Date of Supplement: July 29, 1994

Date of Receipt: July 29, 1994

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,

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

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

~~NDA SUPPLEMENT~~

ORIGINAL

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.

May 10, 1995

SLR-008
FA

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

 **MERCK**
Research Laboratories
NDA SUPPL AMEND

Dear Dr. Sobel:

*6/1/95
OK
[Signature]*

Final Printed Labeling

Supplemental New Drug Application: NDA 19-760

ZOCOR™ (Simvastatin)



Reference is made to the Supplemental New Drug Application S-008 for ZOCOR™ (Simvastatin) submitted on ~~November 10, 1994~~ and an approval letter dated April 19, 1995.

*July 27, 1994
ST per Bob Silverman Merck*

Attached, as requested in the letter of April 19, 1995, are fifteen (15) copies of the final printed package circular (No. 7825415), a Summary of the Revisions and an annotated revised circular.

These changes will become effective on July 1, 1995 and will apply to all packages of ZOCOR™ distributed from the company facilities.

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

Sincerely yours,

[Signature]

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

REVIEWS COMPLETED	
<i>APR 05/17/95</i>	
CSO ACTION:	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I.
Circular No. 7825415	<i>ST 05/23/95</i>
Federal Express #1	DATE

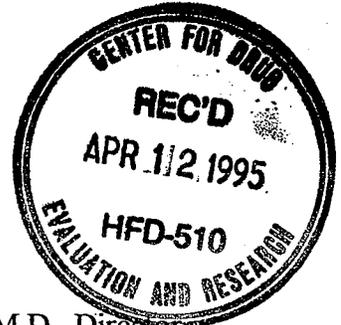
Desk Copy: Dr. S. Trostle, HFD-511, Rm. 14B-04, Federal Express #1

NDA SUPPL AMEND ORIGINAL

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

These copies are
OFFICIAL FDA Copies
not desk copies.

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



April 11, 1995

Solomon Sobel, M.D., Director
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

[Handwritten signature]
mpr 4/14/95
[Handwritten lines]

Dear Dr. Sobel:

Supplemental New Drug Application
NDA 19-766/S-008: ZOCOR
(Simvastatin)

Reference is made to the above Supplemental New Drug Application, (SNDA), originally submitted on July 29, 1994; recommended changes to the proposed labeling from the Agency received by Ms. Dray on April 3, 1995; and an amendment to the SNDA accepting the Agency's recommended labeling changes sent on April 7, 1995.

We have discovered that the April 7 amendment contained a draft circular which requires a correction and a clarification.

Attached is a replacement for page 15 of the draft circular which corrects editorial errors included in the April 7 submission in the PRECAUTIONS section regarding warfarin interactions. The April 7 version of labeling regarding warfarin will be the subject of a future SNDA. In addition, we are clarifying that the April 7 submission included label changes in the DOSAGE AND ADMINISTRATION section (p.22) that were previously approved on February 16, 1995 (NDA 19-766/S-010) but did not appear in the original draft circular enclosed with this SNDA (19-766/S-008) submitted on July 29, 1994.

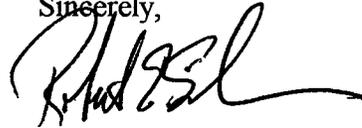
4/17/95
Noted
[Signature]

The above noted correction and clarification to the April 7 draft circular submission are unrelated to the substantive elements of this SNDA. We apologize for any inconvenience or confusion that we may have caused by our mistakes in the April 7 amendment.

We consider this information to be a confidential matter, and request that 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.

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,



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

mcs/q/tr191

Attachment

Via Fax and Federal Express #1

Desk Copy: Dr. S. Aurecchia, HFD-510, Rm. 14B-04, Via Fax and Federal Express #1
Mr. S. Trostle, HFD-510, Rm. 14B-04, Via Fax and Federal Express #1

REVIEWS COMPLETED	
AP 04/19/95	
CSO ACTION:	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I.
ST 04/24/95	
CSO INITIALS	DATE

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

ORIGINAL

These copies are OFFICIAL FDA Copies
not desk copies.

SLR 00834
~~NDA SUPPL AMEND~~
Merck & Co., Inc.
BLA-30
West Point PA 19486
Fax 610 397 2335
Tel 610 397 2944
215 652 5000

~~NDA NO. 19766-REF. NO. 00834~~

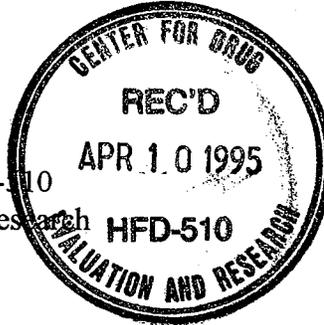
~~NDA SUPPL FOR SLR~~

April 7, 1995



~~NDA SUPPL AMEND~~

Solomon Sobel, M.D., Director
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



~~_____~~
mjm 4/14/95

Dear Dr. Sobel:

Supplemental New Drug Application NDA 19-766/S-008
ZOCOR (Simvastatin)

Reference is made to the above Supplemental New Drug Application, NDA 19-766/S-008 for ZOCOR, originally submitted on July 29, 1994 and recommended changes to the proposed labeling from the Agency received by Ms. Dray on April 3, 1995.

Merck Research Laboratories accepts the labeling recommendations from the Agency and, herein, amends the SNDA to incorporate the April 3 recommended language. Attached is an amended draft of the product circular. Please note that the "new graphs" included in the original SNDA label proposal are retained with this amendment although they are not reproduced in the draft circular attached.

As required by Section 306 (k)(1) of the Generic Drug 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 amendment to the Supplemental New Drug Application 19-766/S-008 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.

Approved
4/13/95
[Signature]

Dr. Solomon Sobel, M.D.
April 7, 1995
Page 2

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,



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

jc/q/ltz/186

Federal Express # 3945719481

Desk Copies: Dr. Steven A. Aurecchia, HFD-510, Rm. 14B-04
Federal Express No. 2589291261
Dr. Stephen T. Trostle, HFD-510, Rm. 14B-04
Federal Express No. 2589291272

REVIEWS COMPLETED	
RP 04/19/95	
CSO ACTION:	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I.
ST 04/24/95	
CSO INITIALS	DATE

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

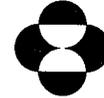
SLR-008 88

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**
not desk copies.

January 19, 1995

ORIGINAL



MERCK
Research Laboratories

Solomon Sobel, M.D., Director
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

REVIEW'S COMPLETED
AP 04/14/95
ST 04/24/95
 N.A.I.

Dear Dr. Sobel:

Amendment to Supplemental New Drug Application
NDA 19-766/S-008 ZOCOR (MAAS)
(Simvastatin)

Reference is made to the above Supplemental New Drug Application proposing a change in the ZOCOR label related to the Monitored Atherosclerosis Regression Study (MAAS); a telephone conversation between Dr. Silverman and Ms. Mele on January 5, 1995; and a telefax from Ms. Mele on that day requesting additional information on the MAAS.

By this amendment, Merck Research Laboratories (MRL) is providing responses to Ms. Mele's requests. Requests #1-3 are derived from Ms. Mele's telefax (copy provided as Attachment 1) and request #4 was made during the aforementioned telephone conversation.

FDA Request #1: Please send a dataset containing data from the MAAS.....

MRL Response: The requested data in the form of a SAS dataset on a 3.5 inch high density micro-diskette is provided as Attachment 2. Attachment 3 contains, in hard copy, a supplemental explanation of the dataset, a PROC CONTENTS of the dataset and a sample of 30 observations from the dataset. ✓

FDA Request #2: Please send descriptive statistics for the primary efficacy variables.....by center and treatment group. ✓

MRL Response: Attachment 4 provides the requested statistics. ✓

FDA Request #3: Please provide the necessary information to complete the table below.....this table provides additional information about the time of patient withdrawal. ✓



MRL Response: The completed table is provided in Attachment 5.

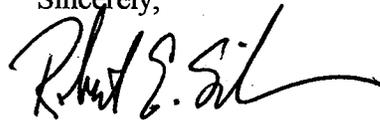
FDA Request #4: Please provide a copy of the reference cited in the CSR Synopsis for MAAS contained in the SNDA (Oliver, Lancet 339, 1241 (1992)).

MRL Response: A copy of the requested reference is provided in Attachment 6.

We consider the information included in this amendment to SNDA 19-766/S-008 to be a confidential matter, and request that 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.

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,



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

mcs/q/ltr/161

Attachment

Federal Express # 2589291994

Desk Copy: (w/o att.) Dr. S. Aurecchia, HFD-510, Rm. 14B-04

Federal Express # 2589291994

(w/att.) Ms. J. Mele, HFD-713, Rm. 18B-45

Federal Express # 2589291994

(w/o att.) Mr. S. Trostle, HFD-510, Rm. 14B-04

Federal Express # 2589291994

2/2/95
noted
(N/AE)
AA

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

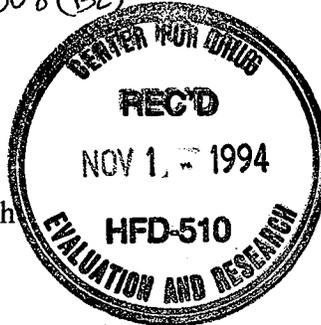
These copies are OFFICIAL FDA Copies
not desk copies.

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

October 27, 1994

NDA SUPPL AMEND
SLR-008(BL)

Solomon Sobel, M.D., Director
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Dear Dr. Sobel:

Supplemental New Drug Application
NDA 19-766/S-008: ZOCOR (MAAS)
(Simvastatin)

*noted
EKB
11/2/94*

Reference is made to the above Supplemental New Drug Application, SNDA 19-766/S-008, submitted July 29, 1994 which requests new product labeling related to the Multicenter Anti-Atheroma Study (MAAS). By copy of this letter, we are providing a copy of the recently published manuscript of MAAS (MAAS Investigators, Lancet, Vol. 344, pp 633-638, September 3, 1994, attached).

We trust this information is helpful. If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

ORIGINAL

Sincerely,

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

*11/2/94
AKC
NAI*

mcs/q/ltr/124
Attachment

Certified # P 151 562 900

Desk Copy (w/att.)

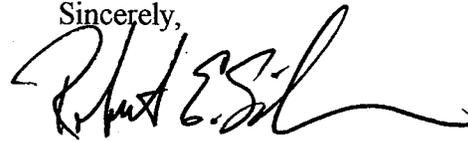
REVIEWS COMPLETED	
<i>AP 04/23/95</i>	
CSO ACTION: <i>5/04/24/95</i>	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I.
CSO INITIALS	DATE

Dr. S. Aurecchia, HFD-510, Rm. 14B-04, Certified # P 151 562 900
Dr. G. Troendle, HFD-510, Rm. 14B-04, Certified # P 151 562 901

We consider the filing of this amendment to the Supplemental New Drug Application 19-766/S-008 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.

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,



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

mcs/q/ltr/114

Federal Express# 2254040751

Desk Copy: Via Fax and hard copy: Dr. S. Aurecchia, HFD-510, Rm. 14B-04, Federal Express # 2254040762
Via Fax and hard copy: Mr. S. Trostle, HFD-510, Rm. 14B-04, Federal Express # 2254040773
Hard Copy only: Dr. G. Troendle, HFD-510, Rm. 14B-04
Federal Express # 2254040795

REVIEWS COMPLETED	
AP 04/19/95	
CSO ACTION:	<input type="checkbox"/> N.A.I.
<input checked="" type="checkbox"/> LETTER	ST 04/24/95
CSO INITIALS	DATE

NDA 19-766 ZOCOR S-008 (MAAS)
Solomon Sobel, M.D.
August 24, 1994

2

Q:cd/letters/MAAS

Attachment
Federal Express No. 1346088461

FAX and Federal Express:
Dr. Gloria Troendle, HFD-510, Rm. 14B-04
Fed.Ex. No. 1346088450

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

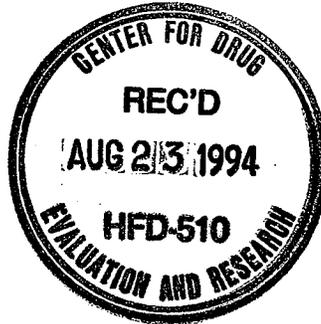
Merck & Co., Inc.
BLA-30
West Point PA 19486
Fax 610 397 2335
Tel 610 397 2944
215 652 5000

These copies are OFFICIAL FDA Copies
not desk copies.

ORIGINAL

August 19, 1994

Solomon Sobel, M.D., Director
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



*center
m/ra 9/8/96*

Dear Dr. Sobel:

NDA 19-766/S-008: ZOCOR
(Simvastatin)

Reference is made to the above Supplemental New Drug Application concerning the results of the Multicenter Anti-Atheroma Study (MAAS) and a telephone conversation between Dr. Silverman and Dr. Aurecchia on August 17, 1994. During the August 17 discussion, Dr. Aurecchia communicated the Agency's concern about part of the S-008 proposal

MRL has provided sufficient information for the Agency to undertake a comprehensive review of the labeling proposal. We are confident that, upon completion of that review,

We trust this information is helpful. If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

REVIEWS COMPLETED	
AP 04/19/95	DATE
CSO ACTION:	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I.
ST 04/24/95	DATE
CSO INITIALS	

Sincerely

[Signature]
Robert E. Silverman, M.D., Ph.D.

*9/7/94
noted
[Signature]*

*noted
ELB
9/12/94*

mcs/q/tr/102
Certified # P 377 419 269

Desk Copy: Dr. Aurecchia HFD-510, Rm. 14B-04, Certified # P 377 419 270
Mr. Tostle HFD-510, Rm. 14B-04, Certified # P 377 419 271

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

NDA NO. 19766 REF. NO. 008
NDA SUPPL FOR SEI

ORIGINAL



July 29, 1994

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

8/10/94
see attached
S.A.



Dear Dr. Sobel:

Supplemental New Drug Application: NDA 19-766
ZOCOR (Simvastatin)

Pursuant to Section 505(b) of the Food, Drug and Cosmetic Act and in accordance with 21 CFR 314.50 and 21 CFR 314.70(b), we submit, for your approval, a supplement to NDA 19-766.

As indicated on the attached Form FDA 356h, this supplemental application provides for additions to Items 4c., 8, 10, 11, 12, and 13 of NDA 19-766 and contains information that supports the addition of new label language for ZOCOR Tablets.

This submission includes the data from the Multicenter Anti-Atheroma Study (MAAS). This Merck-sponsored study is the largest and longest anti-atheroma trial completed to date and provides strong evidence for the beneficial impact of treatment with simvastatin on the progression of coronary atherosclerosis. The results from this trial are consistent with the effects seen in similarly designed studies using other lipid lowering therapies. Therefore, this submission incorporates an overview of MAAS in the context of other completed angiographic studies. In particular, the Canadian Coronary Artery Intervention Trial (CCAIT) and the Monitored Atherosclerosis Regression Study (MARS), Merck-sponsored studies using lovastatin as the lipid lowering agent, will be highlighted as corroborative evidence for MAAS in the overview.

The proposed labeling change in this supplement includes a description of MAAS in the Clinical Studies subsection of the CLINICAL PHARMACOLOGY section; a brief summary of the adverse event experience during MAAS in the Clinical Adverse Experiences subsection of the ADVERSE REACTIONS section;

MOG 8-3-94
MO stated on 10/20/94 (see subm. dated 09/27/94) "OK to file as labeling
re-submission" ST 03/30/95

USER FEE DATA ENTRY/VALIDATION FORM

Ver.3 (2/17/94)

\$40,5k pd 7/26/94

NDA # 19766 DOCUMENT ID/LETTER DATE SEI-008 7-29-94
APPLICANT NAME Merck
PRODUCT NAME Zocor

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 labelling).]

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	FEE	NO FEE
N _____	_____	_____	_____
N _____	_____	_____	_____

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 _____	_____	_____	_____

5. P S

PRIORITY OR STANDARD?

S. Trost 08/02/94

J.M. Gallies 8/2/94

6. CSO SIGNATURE/DATE

SCSO CONCURRENCE SIGNATURE/DATE

COPY DISTRIBUTION: ORIGINAL TO ARCHIVAL AFTER DATA ENTRY, ONE COPY EACH 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

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

Reports Clearance Officer, PHS
Hubert H. Humphrey Building, Room 721-B
200 Independence Avenue, S.W.
Washington, DC 20201
Attn: PRA

and to:

Office of Management and Budget
Paperwork Reduction Project (0910-0297)
Washington, DC 20503

Please DO NOT RETURN this form to either of these addresses.

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: David W. Blois, Ph.D.
Vice President
Worldwide Regulatory Affairs

3. TELEPHONE NUMBER (Include Area Code)

(610) 397-2304

4. PRODUCT NAME

ZOCOR (Simvastatin)

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

1

7. LICENSE NUMBER/NDA NUMBER

N019766

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

David W. Blois
David W. Blois, Ph.D.

TITLE

Vice President
Worldwide Regulatory Affairs

DATE

July 29, 1994