

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**19-643/S-017**

***Trade Name:*** Mevacor Tablets

***Generic Name:*** lovastatin

***Sponsor:*** Merck Sharpe and Dome Research Laboratories

***Approval Date:*** December 19, 1991

***Indications:*** 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 diet restricted in saturated fat and cholesterol and to other nonpharmacological measures alone has been inadequate.

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*APPLICATION NUMBER:*

**19-643/ S017**

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### **Reviews / Information Included in this NDA Review.**

<b>Approval Letter</b>	<b>X</b>
<b>Approvable Letter</b>	<b>X</b>
<b>Labeling</b>	<b>X</b>
<b>Medical Review(s)</b>	
<b>Chemistry Review(s)</b>	
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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**19-643/S-017**

**APPROVAL LETTER**

1911

NDA 19-643/S-017

DEC 19 1991

Merck Sharp and Dohme Research Laboratories  
Attention: Bonnie Goldman, M.D.  
Director, Regulatory Affairs  
Sumneytown Pike  
West Point, PA 19486

Dear Dr. Goldman:

Reference is made to your supplemental new drug application dated June 29, 1990, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mevacor (lovastatin) Tablets.

The supplement provides for changes to the **CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION** sections of the package insert based on clinical data from the Expanded Clinical Evaluation of Lovastatin (EXCEL) study.

We also acknowledge receipt of your amendments dated November 8 and 15, and December 3 and 16, 1991. We further refer to the telephone conversations on November 20 and December 12, 1991, between members of this Division and your office concerning additional modifications to the approved package insert. Additionally, we refer to our supplement approvable letter dated November 5, 1991, requesting further revisions to the current approved labeling.

We have completed our review of this supplemental application and it is approved as amended, effective on the date of this letter.

Please submit twelve (12) copies of the final printed labeling (FPL) identical to the draft labeling as amended to FDA as soon as available. Seven of the copies should be individually mounted on heavy weight paper or similar material. The submission should be designated for administrative purposes as "FPL for Approved NDA 19-643/S-017." Approval of the submission by FDA is not required before the labeling is used. Marketing the product with FPL that is not identical to the draft labeling may render the product misbranded and an unapproved new drug.

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

Should there be any questions regarding this communication, please contact Dr. James Cheever at (301) 443-3520.

Sincerely yours,

*S* 12/18/91  
Solomon Sobel, M.D.  
Director  
Division of Metabolism and  
Endocrine Drug Products, HFD-510  
Center for Drug Evaluation and Research

cc: NDA Arch.  
HFD-510  
HFC-130/JAllen w/ draft labeling  
HFD-19/ w/ draft labeling  
HFD-80/ w/ draft labeling  
HFD-500/LRipper w/ draft labeling  
HFD-638/ w/ draft labeling  
HFD-735/ w/ draft labeling  
HFD-510/RPierce/MThomas/SAurecchia/MRhee/EBarbehenn  
HFD-511/JCheever/12.18.91/N19643AP.S17/FTjrc12.18.91  
Concurrence: SAurecchia, MThomas, RPierce, MRhee, YChiu, EBarbehenn,  
AJordan, 12.18.91  
SUPPLEMENT APPROVAL (S-017)

*MC* 12/18/91

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**19-643/S-017**

**APPROVABLE LETTER**

19.1

NDA 19-643/S-017

NOV 5 1991

Merck Sharp and Dohme Research Laboratories  
Attention: Bonnie Goldman, M.D.  
Director, Regulatory Affairs  
Sumneytown Pike  
West Point, PA 19486

Dear Dr. Goldman:

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The supplement provides for changes to the **CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION** sections of the package insert based on clinical data from the Expanded Clinical Evaluation of Lovastatin (EXCEL) study.

We have completed the review of this supplemental application, including the draft labeling submitted in your June 29 letter, and it is approvable. Before the application may be approved, however, we request that you submit a number of recommended changes to the text as an amendment to this supplement. These changes are noted on the enclosed 3½" disk (Word Perfect) for your convenience and indicated on the accompanying hard copy of the revised package insert. Please note that ~~strikeout~~ indicates previously existing text which has been deleted and that redline indicates new text. The altered package insert is on disk under the file name REV-LAB.001.

Additionally, we request that the following recommendations to the Mevacor package insert be implemented:

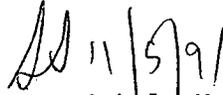
1. ~~1. Please insert the structural formula of lovastatin in the DESCRIPTION section.~~
2. Please insert the structural formula of lovastatin in the **DESCRIPTION** section.
3. ~~3. Please insert the structural formula of lovastatin in the DESCRIPTION section.~~
4. ~~4. Please insert the structural formula of lovastatin in the DESCRIPTION section.~~

We request that these changes be made in the most expeditious manner possible. Please submit the required amendment within 7 days of receipt of this letter. All the changes indicated above cannot be legally implemented until you have been notified in writing that the application is approved.

Many of the recommended changes to the Mevacor package insert are the result of the Division's efforts to implement class labeling for HMG-CoA reductase inhibitors. This process is difficult at best and impossible to accomplish simultaneously for drugs in this class. Please insure that interim product advertising conforms to the new labeling requested in this letter.

Should there be any questions regarding this communication, please contact Dr. James Cheever at (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

2 Enclosures:

3½" disk (Word Perfect)  
Revised package insert

cc: NDA Arch.  
HFD-510  
HFC-130/JAllen  
HFD-80  
HFD-510/RPierce/MThomas/AJordan/EBarbehenn/YChiu/MRhee  
HFD-511/JCheever/11.01.91/ftJRC11.05.91/N19643AE.S17  
Concurrence: JShort, RPierce, AJordan, SAurecchia, YChiu, 11/4/91  
EBarbehenn, 11/5/91  
SUPPLEMENT APPROVABLE (S-017)

*Handwritten note: ne 11/5/91*

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**19-643/S-017**

**LABELING**

**MSD | MEVACOR®**  
(LOVASTATIN)

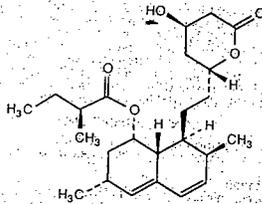
*Mz/3/10*

**MEVACOR®**  
(Lovastatin)

**DESCRIPTION**

MEVACOR® (Lovastatin) is a cholesterol-lowering agent isolated from a strain of *Aspergillus terreus*. After oral ingestion, lovastatin, which is an inactive lactone, is hydrolyzed to the corresponding  $\beta$ -hydroxyacid form. This is a principal metabolite and 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.

Lovastatin is 1[S-(11 $\alpha$ ),3 $\alpha$ ,7 $\beta$ ,8 $\beta$ ](2S\*,4S\*),8 $\beta$ ]-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate. The empirical formula of lovastatin is C<sub>24</sub>H<sub>36</sub>O<sub>5</sub> and its molecular weight is 404.55. Its structural formula is:



*AR*  
*MAR 30*

Lovastatin is a white, nonhygroscopic crystalline powder that is insoluble in water and sparingly soluble in ethanol, methanol, and acetone.

Tablets MEVACOR are supplied as 10 mg, 20 mg and 40 mg tablets for oral administration. In addition to the active ingredient lovastatin, each tablet contains the following inactive ingredients: cellulose, lactose, magnesium stearate, and starch. Butylated hydroxyanisole (BHA) is added as a preservative. Tablets MEVACOR 10 mg also contain red ferric oxide and yellow ferric oxide. Tablets MEVACOR 20 mg also contain FD&C Blue 2. Tablets MEVACOR 40 mg also contain D&C Yellow 10 and FD&C Blue 2.

**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 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.

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

LDL is formed from VLDL and is catabolized predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of MEVACOR 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 MEVACOR. Since each LDL particle contains one molecule of apolipoprotein B and since little apolipoprotein B is found in other lipoproteins, this strongly suggests that MEVACOR does not merely cause cholesterol to be lost from LDL, but also reduces the concentration of circulating LDL particles. In addition, MEVACOR can produce increases of variable magnitude in HDL cholesterol, and modestly reduces VLDL cholesterol and plasma triglycerides (see Tables I-IV under Clinical Studies). The effects of MEVACOR on lipids, fibrogen, and certain other independent biochemical risk markers for coronary heart disease are unknown.

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

**Pharmacokinetics**  
Lovastatin is a lactone which is readily hydrolyzed *in vivo* to the corresponding  $\beta$ -hydroxyacid. Lovastatin is a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the  $\beta$ -hydroxyacid metabolites (active inhibitors) and following hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of lovastatin.

Following an oral dose of <sup>14</sup>C-labeled lovastatin, in man, 10% of the dose was excreted in urine and 83% in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug. Plasma concentrations of total radioactivity (lovastatin plus <sup>14</sup>C-metabolites) peaked at 2 hours and declined rapidly to about 10% of peak by 24 hours postdose. Absorption of lovastatin is estimated relative to an intravenous reference dose. Mean <sup>14</sup>C of four animal species tested averaged about 30% of an oral dose in animal studies after oral dosing lovastatin.

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**MEVACOR®**  
(Lovastatin)

had high selectivity for the liver, where it achieved substantially higher concentrations than in non-target tissues. Lovastatin 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 lovastatin, the availability of drug to the general circulation is low and variable. In a single dose study in four hypercholesterolemic patients, it was estimated that less than 5% of an oral dose of lovastatin reaches the general circulation as active inhibitors. Following administration of lovastatin tablets the coefficient of variation, based on between-subject variability, was approximately 40% for the area under the curve (AUC) of total inhibitory activity in the general circulation.

Both lovastatin and its  $\beta$ -hydroxyacid metabolite are highly bound (>95%) to human plasma proteins. Animal studies demonstrated that lovastatin crosses the blood-brain and placental barriers.

The major active metabolites present in human plasma are the  $\beta$ -hydroxyacid of lovastatin, its 6-hydroxy derivative, and two additional metabolites. Peak plasma concentrations of both active and total inhibitors were attained within 2 to 4 hours of oral administration. While the recommended therapeutic dose range is 20 to 80 mg b.i.d., the majority of inhibitory activity in the general circulation was established by a single-dose study employing lovastatin tablet dosages from 60 to as high as 120 mg. With a once-a-day dosing regimen, plasma concentrations of total inhibitors over a dosing interval achieved a steady state between the second and third days of therapy and were about 1.5 times those following a single dose. When lovastatin was given under fasting conditions, plasma concentrations of total inhibitors were on average about two-thirds those found when lovastatin was administered immediately after a standard test meal.

In a study of patients with severe renal insufficiency (creatinine clearance 10-30 mL/min), the plasma concentrations of total inhibitors after a single dose of lovastatin were approximately two-fold higher than those in healthy volunteers.

**Clinical Studies:**  
MEVACOR has been shown to be highly effective in reducing total and LDL cholesterol in heterozygous familial and non-familial forms of primary 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 continuation of therapy. Single daily doses given in the evening were more effective than the same dose given in the morning, perhaps because cholesterol is synthesized mainly at night.

In multicenter, double-blind studies in patients with familial or non-familial hypercholesterolemia, MEVACOR administered in doses ranging from 20 mg q.p.m. to 40 mg b.i.d. was compared to placebo. MEVACOR 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. In addition, MEVACOR produced increases of variable magnitude in HDL cholesterol (HDL-C), and modestly decreased VLDL cholesterol (VLDL-C) and plasma triglycerides (TRIG.) (see Tables I and IV for dose response results).

**TABLE I**  
**FAMILIAL HYPERCHOLESTEROLEMIA STUDY**  
**DOSE RESPONSE OF MEVACOR**  
(Percent Change From Baseline After 6 Weeks)

DOSAGE	N	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/HDL-C (mean)	TOTAL-C/HDL-C (mean)	TRIG. (median)
Placebo	21	1	-2	+1	-1	0	+3
MEVACOR							
20 mg q.p.m.	20	-18	-19	+10	-26	-24	-7
40 mg q.p.m.	21	-24	-27	+10	-32	-28	-22
10 mg b.i.d.	19	-22	-25	+6	-38	-25	-11
20 mg b.i.d.	20	-27	-31	+12	-38	-24	-18
40 mg b.i.d.	20	-34	-39	+12	-43	-38	-12

MEVACOR was compared to cholestyramine in a randomized open parallel study and to probucol in a double-blind, parallel study. Both studies were performed with patients with hypercholesterolemia who were at high risk of myocardial infarction. Summary results of these two comparative studies are presented in Tables II & III.

**TABLE II**  
**MEVACOR 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. (median)
MEVACOR	27	-27	-32	+8	-31	-34	-21	-21
20 mg b.i.d.	85	-27	-32	+8	-31	-34	-21	-21
40 mg b.i.d.	88	-34	-42	+8	-38	-31	-21	-21
Cholestyramine								
12 g b.i.d.	88	-17	-23	+8	-29	-27	-11	-11

Best Possible Copy

MEVACOR®  
(Lovastatin)

TABLE III  
MEVACOR vs. Probucol  
(Percent Change from Baseline After 14 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. (median)
MEVACOR								
40 mg q.p.m.	47	-25	-32	+9	-38	-31	-37	-18
40 mg q.p.m.	49	-30	-37	+11	-42	-36	-27	-17
40 mg b.i.d.	47	-33	-40	+12	-45	-39	-40	-25
Probucol								
500 mg b.i.d.	97	-10	-8	-23	+26	+23	-13	+1

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study  
MEVACOR was compared to placebo in 8,245 patients with hypercholesterolemia (total cholesterol 240-300 mg/dL [6.2 mmol/L - 7.6 mmol/L]; LDL cholesterol >160 mg/dL [4.1 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. All changes in the lipid measurements (Table IV) in MEVACOR treated patients were dose-related and significantly different from placebo (p<0.001). These results were sustained throughout the study.

TABLE IV  
MEVACOR vs. Placebo  
(Percent Change from Baseline - Average Values Between Weeks 12 and 48)

DOSAGE	N*	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	TRIG. (median)
Placebo	1663	+0.7	+0.4	+2.0	+0.2	+0.6	+4
MEVACOR							
20 mg q.p.m.	1642	-17	-24	+6.6	-27	-21	-10
40 mg q.p.m.	1646	-22	-30	+7.2	-34	-26	-14
20 mg b.i.d.	1646	-24	-34	+8.6	-38	-29	-16
40 mg b.i.d.	1649	-29	-40	+9.5	-44	-34	-19

\*Patients enrolled

**Eye**

There was a high prevalence of baseline lenticular opacities in the patient population included in the early clinical trials with lovastatin. During these trials the appearance of new opacities was noted in both the lovastatin and placebo groups. There was no clinically significant change in visual acuity in the patients who had new opacities reported nor was any patient, including those with opacities noted at baseline, discontinued from therapy because of a decrease in visual acuity.

An interim analysis was performed at 2 years in 192 hypercholesterolemic patients who participated in a placebo-controlled, parallel, double-blind study to assess the effect of lovastatin on the human lens. There were no clinically significant differences between the lovastatin and placebo groups in the incidence, type, or progression of lenticular opacities.

**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. MEVACOR 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 diet alone has been inadequate.

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

$$LDL-C = \text{Total cholesterol} - [0.2 \times (\text{triglycerides}) + HDL-C]$$

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

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

**Classification of Hyperlipoproteinemias**

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

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

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

	LDL Cholesterol mg/dL (mmol/L)	Total Cholesterol mg/dL (mmol/L)
	Initiation Level	Minimum Goal
Without Definite CHD or Two Other Risk Factors*	≥190 (≥4.9)	<160 (<4.1)
With Definite CHD or Two Other Risk Factors*	≥160 (≥4.1)	<130 (<3.4)
		Minimum Goal
		<240 (<6.2)
		<200 (<5.2)

\*Other risk factors for coronary heart disease (CHD) include: male sex, family history of premature CHD, cigarette smoking, hypertension, confirmed HDL-C <35 mg/dL, diabetes mellitus, definite cerebrovascular or peripheral vascular disease, or severe obesity.  
For adult diabetics, a modification of these guidelines is recommended—see: American Diabetes Association Consensus Statement: Role of cardiovascular risk factors in the prevention and treatment of macrovascular disease in diabetes, Diabetes Care 12(8): 573-78, 1989.

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

**CONTRAINDICATIONS**

Hypersensitivity to any component of this medication.  
Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).  
Pregnancy and lactation.

Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of cholesterol biosynthesis pathway are essential components for fetal development, inhibitors of HMG-CoA reductase such as MEVACOR to decrease the synthesis of cholesterol and, possibly, other products of the cholesterol biosynthesis pathway. Lovastatin is contraindicated during pregnancy. Lovastatin 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, lovastatin should be discontinued and the patient should be apprised of the potential hazard to the fetus.

**WARNINGS**

**Liver Dysfunction**

Marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least one year in early clinical trials (see ADVERSE REACTIONS). When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin, and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. In the EXCEL study, increases in serum transaminases over 48 weeks was 0.1% for placebo, 0.1% of 20 mg/post-marketing experience with MEVACOR, symptomatic liver disease has been reported rarely at all dosages (see ADVERSE REACTIONS).

It is recommended that liver function tests be performed during therapy with lovastatin. Serum transaminases, including ALT (SGPT), should be monitored before treatment begins, every 6 weeks during the first 3 months, every 8 weeks during the remainder of the first year, and periodically thereafter (e.g., at approximately 6 month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to three times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations are persistent beyond the discontinuation of the drug.

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 disease or unexplained transaminase elevations are contraindications to the use of lovastatin. As with other lipid-lowering agents, moderate (less than three times the upper limit) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

**Skeletal Muscle**  
Rhabdomyolysis has been associated with lovastatin therapy alone, when combined with immunosuppressive therapy including cyclosporine in cardiac transplant patients, and when combined in non-transplant patients with either gemfibrozil or pre-existing renal insufficiency, usually as a consequence of long-standing diabetes. Acute renal failure from rhabdomyolysis has been seen more commonly with the lovastatin-gemfibrozil combination, and has also been reported in transplant patients receiving lovastatin plus cyclosporine.

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored. Erythromycin-induced rhabdomyolysis has been seen as early as three weeks after initiation of combined therapy with gemfibrozil and lovastatin, but may be seen after several months. For these reasons, it is felt that, in most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefits of combined therapy with lovastatin and gemfibrozil do not outweigh the risks 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

sis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of lovastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with lovastatin 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 CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. The monitoring of lovastatin drug and metabolite levels may be considered in transplant patients who are treated with immunosuppressives and lovastatin.

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

Myalgia has been associated with lovastatin therapy. Transient, mildly elevated creatine phosphokinase levels are commonly seen in lovastatin-treated patients. However, in early clinical trials, approximately 0.5% of patients developed a myopathy, i.e., myalgia or muscle weakness associated with markedly elevated CPK levels. In the EXCEL study (see CLINICAL PHARMACOLOGY, Clinical Studies), five (0.1%) patients taking lovastatin alone (one at 40 mg q.p.m., and four at 40 mg b.i.d.) developed myopathy (muscle symptoms and CPK levels > 10 times the upper limit of normal). 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. Lovastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Most of the patients who have developed myopathy (including rhabdomyolysis) while taking lovastatin were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil or lipid-lowering doses of nicotinic acid. In clinical trials, about 30 percent of patients on concomitant immunosuppressive therapy, including cyclosporine developed myopathy; the corresponding percentages for gemfibrozil and niacin were approximately 5 percent and 2 percent respectively.

Patients with cardiac transplants taking immunosuppressive therapy including cyclosporine concomitantly with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately four times the expected levels. Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered.

**PRECAUTIONS**

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

Lovastatin may elevate 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 lovastatin.

**Homozygous Familial Hypercholesterolemia.** MEVACOR is less effective in patients with the rare, homozygous, familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

**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, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin.** See WARNINGS AND ADVERSE REACTIONS.

**Coumarin Anticoagulants.** In a small clinical trial in which lovastatin was administered to warfarin treated patients, no effect on prothrombin time was detected. However, another HMG-CoA reductase inhibitor has been found to produce a less than two seconds increase in prothrombin time in healthy volunteers receiving low doses of warfarin. Also, bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. It is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin, 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 lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

**Antipyridine.** Because lovastatin had no effect on the pharmacokinetics of antipyridine or its metabolites, interactions of other drugs metabolized via the same cytochrome isozymes are not expected.

**Propranolol.** In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

**Digoxin.** In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

**Other Concomitant Therapy.** Although specific interaction studies were not performed, in clinical studies, lovastatin was used concomitantly with beta-blockers, calcium channel blockers, diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

**Endocrine Function**

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Results of clinical trials with drugs in this class have been inconsistent with regard to their effects on basal and reserve steroid levels. However, clinical studies have shown that lovastatin does not reduce basal plasma cortisol levels or impair adrenal reserve. Also, lovastatin does not reduce basal plasma testosterone levels. In patients with HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG. In the same study, the mean testosterone response to HCG was slightly but not significantly reduced after treatment with lovastatin 40 mg daily for 16 weeks in 21 men. 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 lovastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spiroinactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

**CNS Toxicity.** Lovastatin 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). Vestibulo-cochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis were also seen in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level (C<sub>max</sub>) 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 lovastatin at a dose of 180 mg/kg/day, a dose which produced plasma drug levels (C<sub>max</sub>) which were about 30 times higher than the mean values in humans taking 80 mg/day. Similar optic nerve and CNS vascular lesions have been observed with other drugs of this class.

**Carcinogenesis, Mutagenesis, Impairment of Fertility.** In a 24-month carcinogenicity study in mice, there was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in both males and females at 500 mg/kg/day. This dose produced a fourfold increase in total inhibitory activity of humans given the highest recommended dose of lovastatin (drug exposure was measured as total HMG-CoA reductase inhibitory activity in extracted drug exposures of 0.3 to 2 times that of humans at the 80 mg/day dose). A statistically significant increase in pulmonary adenomas was seen in female mice at approximately 4 times the human drug exposure. (Although mice were given 300 times the human dose [HD] on a mg/kg body weight basis, plasma levels of total inhibitory activity were only 4 times higher in mice than in humans given 80 mg of MEVACOR.) There was an increase in incidence of papilloma in the non-glandular mucosa of the stomach of mice treated at exposures of 1 to 2 times that of humans. The glandular mucosa was not affected. The human stomach contains only glandular mucosa. In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for hepatocellular carcinogenesis in males at drug exposures between 2.7 times that of human exposure at 80 mg/day (doses in rats were 5, 30 and 180 mg/kg/day).

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum 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 significantly increased 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 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 fibroblast hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosome aberration assay in mouse bone marrow.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation were seen in dogs starting at 20 mg/kg/day. Similar findings were seen with another drug in this class. No drug-related effects on fertility were found in studies with lovastatin in rats. However, in studies with a similar drug in this class, there was decreased fertility in male rats treated for 34 weeks at a similar body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation); in rats treated with this same reduced spermatogenic epithelium) was observed. No microscopic changes were observed in the testes from rats of either study. The clinical significance of these findings is unclear.

**Pregnancy Category X.** See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Lovastatin has been shown to produce skeletal malformations at plasma levels 40 times the human exposure (for mouse fetus) and 80 times the human exposure (for rat fetus) based on mg/m<sup>2</sup> surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in either evidence of malformations was noted in rabbits at exposures up to 3 times the human exposure (dose of 15 mg/kg/day, highest tolerated dose). MEVACOR 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 MEVACOR, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

**Nursing Mothers**

It is not known whether lovastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human breast milk and because of the potential for serious adverse reactions in nursing infants, women taking MEVACOR 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 with lovastatin is not recommended at this time.

**ADVERSE REACTIONS**

MEVACOR is generally well tolerated; adverse reactions usually have been mild and transient. Less than 1% of patients were discontinued from controlled clinical studies up to 14 weeks due to adverse experiences attributable to MEVACOR. About 3% of

MEVACOR® (Lovastatin)

MEVACOR® (Lovastatin)

patients were discontinued from extensions of these studies due to adverse experiences attributable to MEVACOR; about half of these patients were discontinued due to increases in serum transaminases. The median duration of therapy in these extensions was 5.2 years.

In the EXCEL study (see CLINICAL PHARMACOLOGY, Clinical Studies), 4.6% of the patients treated up to 48 weeks were discontinued due to clinical or laboratory adverse experiences which were rated by the investigator as possibly, probably or definitely related to therapy with MEVACOR. The value for the placebo group was 2.5%.

Clinical Adverse Experiences

Adverse experiences reported in patients treated with MEVACOR in controlled clinical studies are shown in the table below:

Table with 4 columns: Adverse Experience, MEVACOR (N=813) %, Placebo (N=82) %, Cholestyramine (N=88) %, Probucol (N=97) %.

Laboratory Tests

Marked persistent increases of serum transaminases have been noted (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase (CPK) levels of at least twice the normal value on one or more occasions. The corresponding values for the control agents were cholestyramine, 3 percent and probucol, 2 percent. This was attributable to the noncardiac fraction of CPK. Large increases in CPK have sometimes been reported (see WARNINGS, Skeletal Muscle).

Expanded Clinical Evaluation of Lovastatin

(EXCEL) Study

Clinical Adverse Experiences

MEVACOR was compared to placebo in 8,245 patients with hypercholesterolemia (total cholesterol 240-300 mg/dL [6.2-7.8 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. Clinical adverse experiences reported as possibly, probably or definitely drug-related in 1% in any treatment group are shown in the table below. For no event was the incidence on drug and placebo statistically different.

Table with 5 columns: Adverse Experience, Placebo (N=1663) %, MEVACOR 20 mg q.p.m. (N=1642) %, MEVACOR 40 mg q.p.m. (N=1645) %, MEVACOR 20 mg b.i.d. (N=1646) %, MEVACOR 40 mg b.i.d. (N=1649) %.

Other clinical adverse experiences reported as possibly, probably or definitely drug-related in 0.5 to 1.0 percent of patients in any drug-treated group are listed below. In all these cases the incidence on drug and placebo was not statistically different.

Body as a Whole: chest pain; Gastrointestinal: acid regurgitation, dry mouth, vomiting; Musculoskeletal: leg pain, shoulder pain, arthralgia; Nervous System/Psychiatric: insomnia, paresthesia; Skin: alopecia, pruritus; Special Senses: eye irritation.

Concomitant Therapy

In controlled clinical studies in which lovastatin 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 lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. Preliminary data suggests that the addition of either probucol or gemfibrozil to therapy with lovastatin is not associated with greater reduction in LDL cholesterol than that achieved with lovastatin alone. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil or niacin (nicotinic acid) (see WARNINGS, Skeletal Muscle).

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis, arthralgia; Neurological: dysfunction of cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, 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, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

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

Skin: alopecia.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

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

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, and bilirubin; thyroid function abnormalities.

OVERDOSAGE

After oral administration of MEVACOR to mice the median lethal dose observed was > 15 g/m<sup>2</sup>.

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 5-6 g.

Until further experience is obtained, no specific treatment of overdosage with MEVACOR can be recommended.

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

DOSE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving MEVACOR and should continue on this diet during treatment with MEVACOR. MEVACOR should be given with meals.

The recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 20-80 mg/day in single or divided doses; the maximum recommended dose is 80 mg/day.

Adjustments of dosage should be made at intervals of 4 weeks or more. Doses should be individualized according to the patient's response (see Tables I to IV under CLINICAL PHARMACOLOGY, Clinical Studies for dose response results).

In patients taking immunosuppressive drugs concomitantly with lovastatin (see WARNINGS, Skeletal Muscle), therapy should begin with 10 mg of MEVACOR and should not exceed 20 mg/day.

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

Concomitant Therapy

Preliminary evidence suggests that the cholesterol-lowering effects of lovastatin and the bile acid sequestrant, cholestyramine, are additive.

Dosage in Patients with Renal Insufficiency

In patients with severe renal insufficiency (creatinine clearance < 30 mL/min), dosage increases above 20 mg/day should be carefully considered and, if deemed necessary, implemented cautiously (see CLINICAL PHARMACOLOGY and WARNINGS, Skeletal Muscle).

HOW SUPPLIED

No. 3560—Tablets MEVACOR 10 mg are peach, octagonal tablets, coded MSD 730. They are supplied as follows:

NDC 0006-0730-61 unit of use bottles of 60.

No. 3561—Tablets MEVACOR 20 mg are light blue, octagonal tablets, coded MSD 731. They are supplied as follows:

NDC 0006-0731-37 unit of use bottles of 30.

NDC 0006-0731-61 unit of use bottles of 60.

(6505-01-267-2497) 20 mg 60 tablets.

NDC 0006-0731-94 unit of use bottles of 90.

NDC 0006-0731-28 unit of use packages of 100.

NDC 0006-0731-78 unit of use bottles of 100.

No. 3562—Tablets MEVACOR 40 mg are green, octagonal tablets, coded MSD 732. They are supplied as follows:

NDC 0006-0732-61 unit of use bottles of 60.

(6505-01-310-0615) 40 mg 60 tablets.

NDC 0006-0732-94 unit of use bottles of 90.

Storage: Store between 5-30°C (41-86°F). Tablets MEVACOR must be protected from light and stored in a well-closed, light-resistant container.

Distributed by:

MSD MERCK SHARP & DOHME

DIV OF MERCK & CO., INC., WEST POINT, PA 19386, USA

Manufactured by:

MERCK SHARP & DOHME QUIMICA, DEL PUERTO RICO, INC., Caguas, Puerto Rico 00626. Printed in USA.

Best Possible Copy

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**19-643/S-017**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

NDA 19-643/S-017

Merck Sharp and Dohme Research Laboratories  
Attention: Bonnie Goldmann, M.D.  
Director, Regulatory Affairs  
Sumneytown Pike  
West Point, PA 19486

MAR 30 1992

Dear Dr. Goldmann:

Reference is made to your supplemental new drug application dated June 29, 1990, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mevacor (lovastatin) Tablets.

The supplement provides for changes to the **CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS,** and **DOSAGE AND ADMINISTRATION** sections of the package insert based on clinical data from the Expanded Clinical Evaluation of Lovastatin (EXCEL) study and additional class labeling changes requested by FDA.

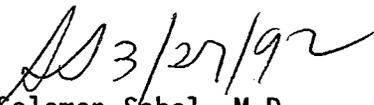
We also acknowledge receipt of your communication dated January 10, 1992, enclosing final printed labeling as requested in our supplement approval letter dated December 19, 1991.

The final printed labeling is being retained for our files.

According to section 502(c) of the Act and 21 CFR 201.15(a)(6), one of the requirements for a package insert is that it be legible. We recommend that a larger typeface be used for the next printing of the Mevacor package insert.

Should there be any questions concerning this communication, please contact Dr. James Cheever at (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: NDA Arch

HFD-510

HFC-130/JAllen w/labeling

HFD-80 w/labeling

HFD-600 w/labeling

HFD-730 w/labeling

HFD-500/LRipper w/labeling

HFD-510/RPierce/MThomas/EBarbehenn/MRhee

HFD-511/JCheever/02.10.92/N19643AR.S17/FTjrc03.26.92

Concurrence: MThomas, 03.17/RPierce, EBarbehenn, AJordan, 03.25/MRhee,  
YChiu, 03.26.92

ACKNOWLEDGE & RETAIN (S-017)

*pe 3/26/92*

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MERCK SHARP & DOHME RESEARCH LABORATORIES

DIVISION OF MERCK & CO., INC.

WEST POINT, PENNSYLVANIA 19486

ORIGINAL

BONNIE J. GOLDMANN, M.D.  
SENIOR DIRECTOR  
REGULATORY AFFAIRS

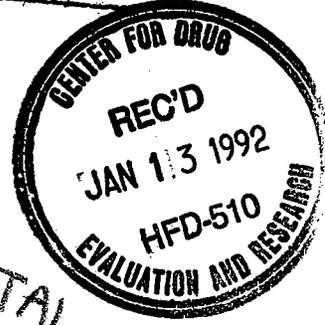
Labeling:

~~NDA No: 19-643~~ ~~Rev'd. S-017~~

~~Reviewed by:~~

(215) 834-2383  
(215) 661-5000

January 10, 1992



SLR/017/FA  
NDA SUPPLEMENTAL  
AMENDMENT

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

Dear Dr. Sobel:

Final Printed Labeling for Approved  
Supplemental New Drug Application: ~~NDA 19-766/S-017~~  
19-643  
Tablets MEVACOR® (Lovastatin)

*noted  
ack  
3/25/92*

*Noted  
3/17/92  
JMB  
3/25/92*

Reference is made to the Supplemental New Drug Application 19-643/S-017 for Tablets MEVACOR® submitted on June 29, 1990. Reference is also made to your letter dated December 19, 1991 approving that application.

The circular has been revised throughout to incorporate class labeling changes requested by the FDA and pertinent data from the EXCEL study.

Attached are twelve (12) copies of the final printed package circular (No. 7526519) as requested in your approval letter.

Questions concerning this supplemental application should be directed to Bonnie J. Goldmann, M.D. (215/834-2383) or, in my absence, David W. Blois, Ph.D. (215/834-2304).

*noted  
mjc, 3/26/92*

Sincerely yours,

*Bonnie J. Goldmann*  
Bonnie J. Goldmann, M.D.  
Senior Director, Regulatory Affairs.

SMK/cat  
57H

Attachments

Circular No. 7526519

Federal Express No. 0535961602

Desk copy: Dr. James Cheever, HFD-511, Room 14B-04  
Federal Express No. 0535961613

MEMORANDUM OF TELECONFERENCE

DECEMBER 12, 1991

NDA 19-643  
MEVACOR (LOVASTATIN)  
MERCK SHARP & DOHME

=====

PURPOSE: To discuss proposed labeling revisions to current circular.

=====

**MERCK REPRESENTATIVES:**

David Blois, Ph.D	Exec. Director, U.S. Regulatory Affairs
Dale Mitchell, M.D.	Clinical Research
Bonnie Goldmann, M.D.	Regulatory Liaison

**FDA REPRESENTATIVES:**

Dr. Sobel  
Dr. Pierce  
Dr. Cheever CSO

=====

**DISCUSSION:**

1. The discussion centered around the Agency's requested changes to their proposed labeling revisions.
2. The simple editorial changes were found to be mutually acceptable.
3. Agreements reached included:
  - a. Antipyrine section language acceptable.
  - b. Coumarin drug interaction section change the word to the mean +/- SD values in seconds for the prolongation of prothrombin time.

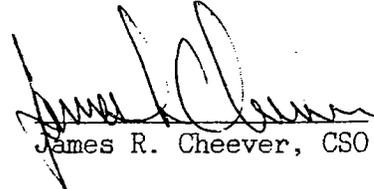
c. In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for hepatocellular carcinogenicity in males at drug exposures between 2 / 7 times that of humans at 80 mg/day (doses in rats were 5, 30, and 180 mg/kg/day).

to "increased".

3. A specific point of contention was not reconciled; it dealt with the descriptive modifier /
- =====

CONCLUSIONS:

1. Merck will submit an amendment that incorporates the agreed upon changes to the proposed labeling.
2. *h*

 12/14/91  
James R. Cheever, CSO

cc: NDA Arch  
HFD-510  
HFD-510/SSobel/RPierce/MThomas/SAurecchia/AJordan/EBarbehenn  
HFD-511/JCheever/12.12.91/N19643TC.004/jrc12.16.91  
Concurrences: RPierce,12.11/SSobel,12.12.91

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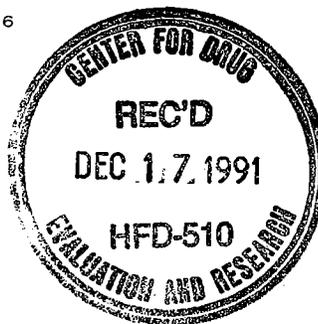
MERCK SHARP & DOHME RESEARCH LABORATORIES

DIVISION OF MERCK & CO., INC.

WEST POINT, PENNSYLVANIA 19486

BONNIE J. GOLDMANN, M.D.  
SENIOR DIRECTOR  
REGULATORY AFFAIRS

December 16, 1991



(215) 834-2383  
(215) 661-5000

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

Dear Dr. Sobel:

017  
NDA 19-643/S-019: MEVACOR®  
(Lovastatin, MSD)

ORIGINAL  
SLR/019/BL  
NDA SUPPL AMENDMENT

Reference is made to the above Supplemental New Drug Application, several telephone conversations, and submission concerning the supplement and class labeling for MEVACOR. Reference is also made to a teleconference on December 11, 1991 between FDA and MSDRL.

By copy of this letter, MSDRL agrees to all the changes discussed during the teleconference on December 11, 1991. These changes in CLINICAL PHARMACOLOGY, PRECAUTIONS, Drug Interactions - Coumarin section, and PRECAUTIONS, Carcinogenesis/Mutagenesis/Impairment of Fertility are shown in the attached Summary of Revisions. The requested revisions are highlighted by redlining and strikeout.

We trust this information is helpful. If you have any questions or need additional information please contact Bonnie J. Goldmann, M.D., (215/834-2383) or, in my absence, David W. Blois, Ph.D., (215/834-2304).

Sincerely,

*Bonnie J. Goldmann*  
Bonnie J. Goldmann, M. D.

cd/1383I  
Attachment  
Federal Express No. 2943349113

Desk Copies and Facsimile: Dr. James Cheever, HFD-510  
Federal Express No. 2943349113

REVIEWS COMPLETED  
AP 12/19/91  
CSO ACTION:  
 LETTER  NAL  
CSO INITIALS *ll* DATE 12/23/91

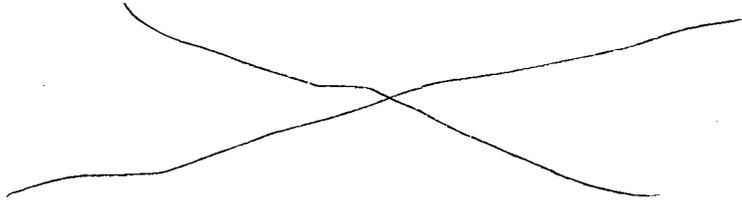
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DEC 11 1991

GROUP LEADER'S REVIEW OF AMENDMENT TO APPROVABLE LABELING SUPPLEMENT

DRUG: MEVACOR (LOVASTATIN)  
NDA: 19643  
SPONSOR: MERCK  
DATE OF SUBMISSION: 12-3-91  
DATE OF REVIEW: 12-11-91

Merck has submitted revised labeling containing changes agreed to during our 11-20-91 teleconference. Most of these changes are satisfactory,

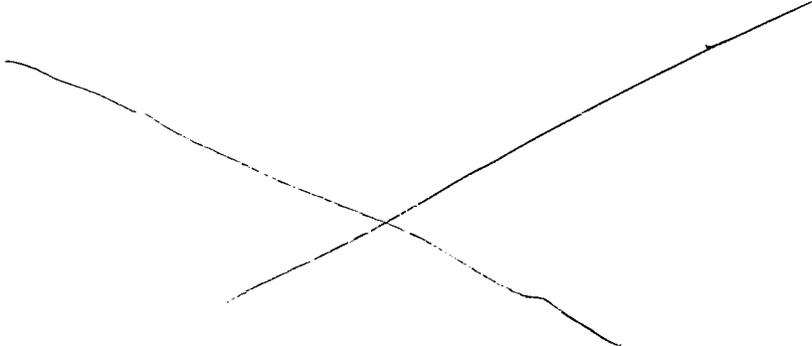


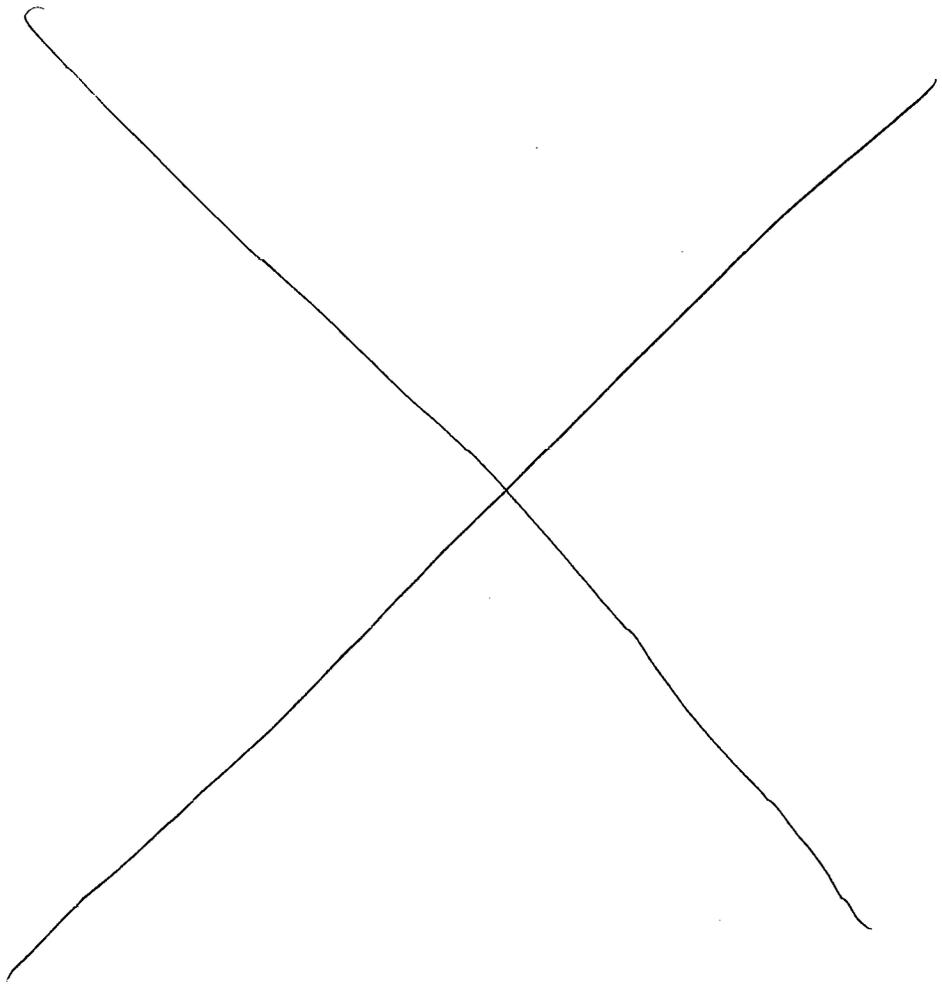
The sponsor states that three areas were unresolved during the 11-20-91 teleconference:

1. The wording regarding antipyrine under Precautions, Drug Interactions. The sponsor's present proposal is acceptable, as it is now specific to the same cytochrome isozymes that metabolize antipyrine.

2. Precautions, Drug Interactions-Coumarin.

mean +/-SD values in seconds for the prolongation of the prothrombin time observed in the study with the other related drug (simvastatin).





RECOMMEND: Retain the descriptor

*Ross Pierce, MD*  
Ross Pierce

\* preliminary data.

cc  
NDB  
HFD 510  
HFD 510/Pierce/Sobel/Cheever/Aurecchia  
[mevlabf.wp]

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MERCK SHARP & DOHME RESEARCH LABORATORIES  
DIVISION OF MERCK & CO., INC.  
WEST POINT, PENNSYLVANIA 19486

ORIGINAL

BONNIE J. GOLDMANN, M.D.  
SENIOR DIRECTOR  
REGULATORY AFFAIRS

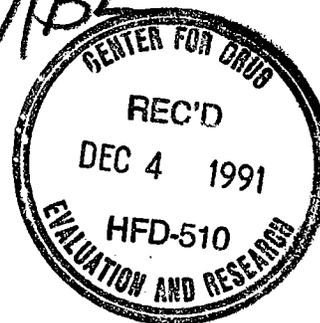
December 3, 1991

(215) 834-2383  
(215) 661-5000

NDA SUPPL AMENDMENT

SLR/017/BL

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



Dear Dr. Sobel:

NDA 19-643/S-017: MEVACOR  
(Lovastatin, MSD)

Reference is made to the above supplement and an approvable letter received on November 5, 1991 which contained labeling revisions concerning the supplement and class labeling for the HMG CoA reductase inhibitors. Reference is also made to several telephone conversations between FDA and MSDRL. Specific reference to revised draft labeling submitted to FDA dated November 15, 1991, as well as a teleconference between MSDRL and FDA on November 20, 1991 in which this draft was discussed.

Since the teleconference of November 20, 1991, three outstanding issues remain:

- the description under PRECAUTIONS, Drug Interactions - Antipyrine;
- the description under PRECAUTIONS, Drug Interactions - Coumarin.

It should be noted that since the November 20, 1991 teleconference, the issue concerning the MSD housemark has been resolved within MSDRL, i.e. a position consistent with that originally proposed by FDA. Specifically, MSDRL commits to remove the MSD housemark following the generic name. As discussed during a telephone conversation with Dr. Cheever on November 27, 1991, the housemark will be removed from the package circular by 2Q92. MSDRL is committed to removing the housemark from the cartons and bottle and carton labels as soon as it is feasible; however, this cannot be accomplished by 2Q92 and will be phased in.

REVIEWS COMPLETED

CSO ACTION:

LETTER     N.A.I.

APPROVED

CSO INITIALS

DATE

12/11/91

Solomon Sobel, M.D, Director

NDA 19-643/S-017

Page 2

By copy of this letter, submitted for your review is the hard copy and the disk containing the package circular with all agreed upon revisions folded into the body of the package circular; outstanding issues are highlighted. A Summary of Revisions is also provided which contains a listing of the changes folded into the label for ease of review.

We trust this information is helpful. We will contact your office shortly for your concurrence. If you have any questions or need additional information please contact Bonnie J. Goldmann, M.D., (215/834-2383) or, in my absence, David W. Blois, Ph.D., (215/834-2304).

Sincerely,



Bonnie J. Goldmann, M. D.

cd/1372I

Attachments

Federal Express No. 2943349290

Desk Copies (4) and Disk: Dr. James Cheever, HFD-510, Rm. 14B03  
Federal Express No. 2943349301

Div

Cheever

MEMORANDUM OF TELECONFERENCE

NOVEMBER 20, 1991

MEVACOR (LOVASTATIN)  
MERCK SHARP & DOHME  
NDA 19-643

=====

PURPOSE: To discuss proposed labeling revisions to current circular.

=====

**MERCK REPRESENTATIVES:**

David Blois, Ph.D	Exec. Director, U.S. Regulatory Affairs
Jonathan Tobert, M.D.	Exec. Director, Clinical Research
James MacDonald, Ph.D.	Exec. Director, Safety Assessment
Geraldine Mantell, M.D.	Director, Clinical Research
Bonnie Goldmann, M.D.	Regulatory Liaison

**FDA REPRESENTATIVES:**

Dr. Sobel  
Dr. Pierce  
Dr. Aurecchia  
Dr. Barbehenn  
Dr. Cheever CSO

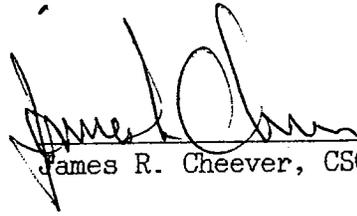
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DISCUSSION:

1. The discussion centered around the firm's requested changes to our proposed labeling revisions.
  2. The majority of the simple editorial changes were found to mutually acceptable.
  3. Specific points of contention were reconciled except for two particular sections:
    - a. The use of the MSD housemark in the generic name.
    - b. )
- =====

CONCLUSIONS:

1. Merck will submit an amendment that incorporates the agreed upon changes to the proposed labeling.
2. Merck will discuss with Dr. Bilstad and Dr. Kumkumian the Agency's policy regarding the use of housemarks in generic drug names.
3. /

 12/3/91  
James R. Cheever, CSO

cc: NDA Arch  
HFD-510  
HFD-510/SSobel/RPierce/SAurecchia/AJordan/EBarbehenn/YChiu/MRhee  
HFD-511/JCheever/11.21.91/N19643TC.003/jrc12.3.91  
Concurrences: JShort, SAurecchia, RPierce, EBarbehenn, SSobel, 12/2/91

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MERCK SHARP & DOHME RESEARCH LABORATORIES

DIVISION OF MERCK & CO., INC.

WEST POINT, PENNSYLVANIA 19486

REVIEWS COMPLETED

*noted further changes agreed to by firm in 11/20/91 tele.*

BONNIE J. GOLDMANN, M.D.  
SENIOR DIRECTOR  
REGULATORY AFFAIRS

CSO ACTION:

LETTER

NAL

NDA SUPPL AMENDMENT  
SLR/017/BL

(215) 834-2383  
(215) 661-5000

CSO INITIALS

DATE

12/23/91

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Products,  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857



*next time  
11/25/91*

NDA 19-643/S-017: MEVACOR  
(Lovastatin, MSD)

Dear Dr. Sobel:

Reference is made to the above Supplemental New Drug Application dated June 29, 1990 and to your letter dated November 5, 1991 in which you advised us that this Supplemental Application is approvable; however, you requested that we submit a number of changes to the text of the draft labeling submitted in our June 29, 1990 submission.

With this letter and the attached revised draft package circular, we are amending our Supplemental Application. Please note that almost all of the revisions requested by the Agency have been incorporated into the revised draft labeling. However, in some cases, editorial changes have been made which we feel add clarity to the information provided. These changes are noted in the right hand column and, where appropriate, we have provided annotations to the data supporting our proposed wording.

In regard to request #4 in your November 5, 1991 letter, please refer to a telephone conversation on November 8, 1991 with Dr. Steven Aurecchia in which we agreed to provide a table of those adverse reactions which occurred in the EXCEL study, at a frequency of greater than 1% in which the adverse reaction was attributable to the drug. This table may be found on page 18 of the package circular.

On page 19 of this circular, line 3 through 20, we note that you have requested that we include in this section of class labeling, five adverse reactions which have not been included in the approved package circular for Pravachol (pravastatin). These adverse reactions are the following: arthralgia, anxiety, insomnia, depression, and alopecia. We have incorporated these into the revised package circular for MEVACOR, with the express understanding that they would be included in the package circular for Pravachol and all other approved HMG CoA reductase inhibitors at the earliest possible opportunity.

*noted - writing to see changes promised. EMB 12/2/91*

*noted MJC 12/2/91*

ORIGINAL

Solomon Sobel, M.D., Director  
NDA 19-643/S017: MEVACOR  
Page 2

We also note that the package circular for Pravachol contains a explicit reference to lovastatin in the section entitled "Skeletal Muscle." We respectfully request, consistent with the concept of class labeling, that individual compounds not be mentioned in other product circulars, rather the reference be made to generic "another HMG CoA reductase inhibitor." We request that the reference to lovastatin in the Pravachol package circular be removed as soon as possible.

Attached is the revised annotated draft package circular, a 3 1/2" computer disk containing the Word Perfect version of this revised circular, and a one page summary entitled "Adverse Experiences Resulting in Discontinuation From Long Term Extension Studies with MEVACOR."

We trust this information is helpful and would welcome a telephone conference or meeting at the earliest possible opportunity to resolve any outstanding labeling issues. If you have any questions or need additional information, please contact Bonnie J. Goldmann, M.D. (215/834-2383), or in my absence, David W. Blois, Ph.D. (215/834-2304).

Sincerely,

*David W. Blois /lor*

Bonnie J. Goldmann, M.D.  
Senior Director  
Regulatory Affairs

/rjp/3470B

Attachments  
Federal Express No. 7902181405

Desk copy with 3-1/2" disk:  
Dr. James Cheever, HFD-510, Room 14B-03  
Federal Express No. 7092181416

MEMORANDUM TO FILE

NDA 19-643  
MEVACOR

NOVEMBER 12, 1991

LETTER TO FDA COMMISSIONER FROM JOSEPH G. HATTERSLEY, M.A.

NO ANSWER REQUIRED.

*JR* 11/2/91  
JAMES R. CHEEVER, CSO

cc: NDA Arch  
HFD-SIO

**ROUTING AND TRANSMITTAL SLIP**

Date

9/23/91

TO: (Name, office symbol, room number, building, Agency/Post)

Initials

Date

1	John	JH	9/23/91
2	Chew	NC	9/23/91
3	R. Pierce	RP	9/23/91
4	S. Aurecchia	SA	10/28/91
5			

Action	File	Note and Return
Approval	For Clearance	Per Conversation
As Requested	For Correction	Prepare Reply
Circulate	<input checked="" type="checkbox"/> For Your Information	See Me
Comment	Investigate	Signature
Coordination	Justify	

**REMARKS**

Do. Robert has been  
logged in - I will  
do you

Please return to me.  
Thanks JH  
9/23/91

DO NOT use this form as a RECORD of approvals, concurrences, disposals, clearances, and similar actions

FROM: (Name, org. symbol, Agency/Post)

Room No. — Bldg.

Lil

5041-102

U.S. GPO: 1989-304-000

Jim  
Please put into  
Newcomer NDA -  
Thanks  
JH  
11/8/91

OFFICE OF THE COMMISSIONER  
EXECUTIVE CORRESPONDENCE

*To Mr. Stewart*

DATE: 91/09/13

FDA TRAC NUMBER: 9104545

PHS TRACER NUMBER:

DATE OF INCOMING: 91/09/13

FROM: HATTERSLY, JOSEPH

AFFILIATION:

SUBJECT: STATEMENT: MEVACOR DISASTROUS UNRECOGNIZED SIDE EFFECTS

ASSIGNED: HFD1 ACTION: NECESSARY ACTION DUE DATE: NONE

*HFD-510 FYI*

COORDINATE WITH:

COMMENTS:

COPIES TO:

EXECUTIVE SECRETARIAT CONTACT: *BETH CLARKE*

HF-43

ROOM 16-70 TELEPHONE (301)443-3900

RECEIVED

SEP 12 3 16 PM '92

EXECUTIVE SECRETARIAT

Mevacor's Disastrous Unrecognized Side Effects

Joseph G. Hattersley, M.A.

September 8, 1991

The most widely used cholesterol-lowering drug is Mevacor, or lovastatin. The drug has serious effects not recognized by the cardiologists who use it or by the Food and Drug Administration, which approved its use without long-term safety tests [1].

The mechanism by which Mevacor lowers cholesterol is weakening of HMG co-A reductase. That mechanism also (1) weakens synthesis of Coenzyme Q10, which is required for cardiac function [2]. In Karl Folkers' test with heart patients, every patient's condition worsened on Mevacor. One was referred for heart transplant; her life was saved with CoQ10 instead [idem].

That mechanism has two other effects, which help explain the patients' worsening. (2) It promotes artery damage, and (3) it interferes with the action of macrophages, the large scavenger white blood cells that attack and destroy invading organisms [3]. It thus weakens the immune system's ability to protect patients against infectious diseases including HIV, the precursor of AIDS.

Medical school provides little or no training in research techniques. Too many cardiologists specialize so narrowly that they read only research published by other cardiologists. That is their idea of research. Kilmer McCully, M.D. is helping me compose a short article for the Journal of the American College of Cardiology, bringing out the adverse side effects of Mevacor.

The value of lowering cholesterol itself, for all but the few with inherited familial hypercholesterolemia (FH) has in fact been questioned [4].

Compare now one completed action of the FDA, the hasty approval of Mevacor and the proposed removal of CoQ10 from ready access by requiring prescription.

Both actions are understandable in light of the conflict of interest among 150 or more high FDA officials who own pharmaceuticals company stocks. Mevacor isn't a drug that you take for 10 days until the bottle is empty. Rather, it is taken for decades. Thus it boosts the profits and the stock price of its maker and increases the wealth of holders of the stock.

The only possible justification for removing CoQ10 from the market would be a finding that some might hurt themselves by taking too much. But Karl Folkers, probably the greatest authority on it, reported that "CoQ10 has no known side effects at any dose level" (personal communication 1991). Getting CoQ10 into

9104545

the clutches of the drug companies, doubtless at several times higher prices, will have the same effect on drug-company profits as the approval of Mevacor.

In both cases, the welfare of patients is harmed. But in the eyes of top FDA officials, their personal profit from owning the stocks seems to outweigh even the most drastic potential harm to patients, which these officials would like to sweep under the rug.

References cited:

- [1] Moore, T.J. (1989), The cholesterol myth, Atlantic September:37-70.
- [2] Folkers, K. et al (1990), Lovastatin decreases coenzyme Q levels in humans, Proc. Nat. Acad. Sci. U.S.A. 87:8931-8934.
- [3] Hill, J.C. et al (1984), Effects of cholesterol autoxidation derivatives on hexose transport in cultured aortic smooth muscle cells, Exp. Molec. Pat. 41:249-257.
- [4] Hattersley, J.G. (1991), Acquired atherosclerosis: Theories of causation, novel therapies, J. Orth. Med. 6:83-98.

Joseph G. Hattersley  
7031 Glen Terra Court S.E.  
Olympia, WA 98503-7119  
(206) 491-1164

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MERCK SHARP & DOHME RESEARCH LABORATORIES

DIVISION OF MERCK & CO., INC.  
WEST POINT, PENNSYLVANIA 19486

ORIGINAL

BONNIE J. GOLDMANN, M.D.  
SENIOR DIRECTOR  
REGULATORY AFFAIRS

November 8, 1991

(215) 834-2383  
(215) 661-5000

LR  
S 07-BM

NDA SUPPL AMENDMENT

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



Noted  
11/15/91  
X

Dear Dr. Sobel:

NDA 19-643: MEVACOR/S-017  
(Lovastatin, MSD)

Reference is made to the above Supplemental New Drug Application and an approvable letter received November 5, 1991. Reference is also made to a telephone conversation on November 8, 1991 between Drs. Steven Aurecchia and Bonnie Goldmann in which the labeling changes proposed by FDA under ADVERSE REACTIONS, Expanded Clinical Evaluation of Lovastatin (EXCEL) Study were discussed.

It was discussed that including all adverse experiences (rather than only those considered drug-related) which occurred during a clinical study of this size (8,425 patients) and duration (48 weeks) would lead to pages of listings of adverse reactions. It is MSDRL's position that these lists would not provide meaningful information to the prescribing physician. Dr. Aurecchia requested that we provide an example of such a table of adverse experiences. By copy of this letter, we are providing a table with all adverse experiences with an incidence of  $\geq 1\%$ . This information was included in the original supplement.

We trust this information is helpful. If you have any questions or need additional information please contact Bonnie J. Goldmann, M.D., (215/834-2383) or, in my absence, David W. Blois, Ph.D., (215/834-2304).

REVIEWS COMPLETED  
12/19/91

Sincerely,

CSO ACTION:

LETTER

N.A.I.

Bonnie J. Goldmann, M. D.

cd/1357I  
Attachment  
Federal Express No. 2943348822

12/23/91

Noted  
11/15/91  
[Signature]

Desk Copy and Fax: Dr. Steven Aurecchia, HFD-510, Rm. 14B26  
Federal Express No. 2943348833



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

Date JUL 6 1990

NDA No.

Attention: *Wanda J. Grindberg, L.R.*

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: *Tablets Mevacor (Lovastatin, MSD)*

NDA Number: *12-643*

Supplement Number: *S-017*

Date of Supplement: *June 29, 1990*

Date of Receipt: *July 1, 1990*

All communications concerning this NDA should be addressed as follows:

*Center for Drug Evaluation and Research (HFD-510)*  
*Center for Drugs and Biologics, HFN-810*  
Attention: Document Control Room 14B-03  
5600 Fishers Lane  
Rockville, MD 20857

**Best Possible Copy**

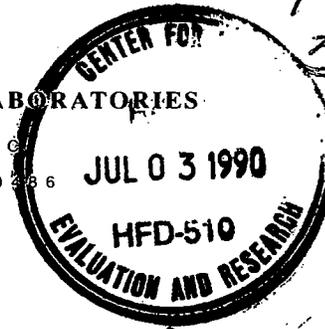
Supervisory Consumer Safety Officer  
Division of Metabolism and Endocrine Drug Products  
Center for Drugs and Biologics

cc:  
NDA-File  
HFN-810 File  
CSO File

19-643  
510

MERCK SHARP & DOHME RESEARCH LABORATORIES

DIVISION OF MERCK & CO., INC.  
WEST POINT, PENNSYLVANIA 19386



NDA NO. 19643 REF. NO. 5017  
NDA SUPPL FOR SOP June 29, 1990

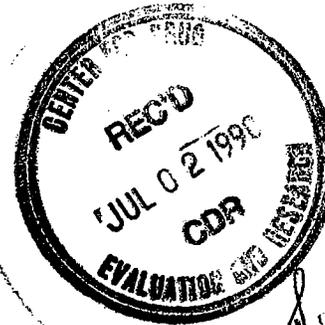
BONNIE J. GOLDMANN, M.D.  
DIRECTOR  
REGULATORY AFFAIRS

approved 12-19-91.

(215) 834-2383  
(215) 661-5000

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

*noted  
exp  
6/24/93*



*noted  
MM 6/24/93*

*This Supplement has been reviewed  
10/25/91 and approved  
12/19/91  
6/24/93*

Dear Dr. Sobel:

Supplemental New Drug Application: NDA 19-643  
Tablets Mevacor® (Lovastatin, MSD)

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 19-643.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in Item 4.c. of the approved New Drug Application for Tablets Mevacor®.

This supplement contains a draft annotated package circular which has been revised throughout to add appropriate data from the Expanded Clinical Evaluation of Lovastatin (EXCEL) study. The clinical study report for the EXCEL study is provided as supportive information.

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

Questions concerning this supplemental application should be directed to Bonnie J. Goldmann, M.D. (215/834-2383) or, in my absence, to David W. Blois, Ph.D. (215/834-2304).

REVIEWS COMPLETED	
SLR/017	AP 12-19-91
CSO ACTION:	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I.
ST	06/30/93
CSO INITIALS	DATE

Sincerely yours,

*Bonnie J. Goldmann*  
Bonnie J. Goldmann, M.D.  
Director, Regulatory Affairs

WL/cat  
4371H

Attached