

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 019643/S051/S053

Trade Name: MEVACOR TABLETS

Generic Name: LOVASTATIN

Sponsor: MERCK RESEARCH LABORATORIES

Approval Date: 06/25/97

Indication(s): HYPOCHOLESTEROLEMIC AGENT

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 019643/S051/S053

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 019643/S051/S053

APPROVAL LETTER

NDA 19-643/S-051

JUN 25 1997

Merck Research Laboratories
Attention: Robert E. Silverman, M.D., Ph.D.
P.O. Box 4, BLA-20
Sumneytown Pike
West Point, PA 19486

Dear Dr. Silverman:

Please refer to your supplemental new drug application dated January 6, 1997, received January 10, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MEVACOR™ (lovastatin) Tablets.

The User Fee goal date for this application is July 10, 1997.

The supplemental application provides for the deletion of two raw material controls from the drug substance manufacturing process,

We have completed the review of this supplemental application and it is approved.

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

If you have any questions, please contact Ms. Margaret Simoneau, Consumer Safety Officer, at 301-443-3510.

Sincerely yours,

/S/

6/25/97

APPEARS THIS WAY

Stephen K. Moore, Ph.D.
Chemistry Team Leader I, DNDC II
Division of Metabolic and Endocrine Drug
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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ON ORIGINAL

NDA 19-643/S-051

Page 2

cc:

Original NDA 19-643
HFD-510/Div. Files
HFD-510/CSO/MSimoneau
HFD-510/ WBerlin/SMoore
HFD-820/ONDC Division Director
HFD-92/DDM-DIAB
DISTRICT OFFICE

APR 24 1997
6:11 PM

Drafted by: Jweber/6/23/97/N19643.051

Initialed by: WBerlin 6/24/SMoore 6/24/EGalliers 6/24/97

final: JWeber/6/24/S/

APPROVAL (AP)

APPEARS THIS WAY
ON ORIGINAL

NDA 19-643/S-053
NDA 19-643/S-050

APR 22 1998

Merck & Co., Inc.
Attention: Charles Hyman, M.D.
P.O. Box 4
West Point, PA 19486

Dear Dr. Silverman:

Please refer to your supplemental new drug application (S-053) dated September 18, 1997, received September 19, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70(c) for Mevacor (Lovastatin) tablets.

The supplemental application contains final printed labeling (#7825339) that was implemented on or about November 1, 1997. Supplement-053 provides for changes in the WARNINGS/ Skeletal Muscle and PRECAUTIONS/ Drug Interactions sections of the Mevacor package insert. These include:

WARNINGS, Skeletal Muscle

1. The word "cardiac" used to describe transplant patients with rhabdomyolysis resulting from concomitant immunosuppressant therapy has been deleted.
2. Ketoconazole has been added to the paragraph describing the interaction with itraconazole.
3. The macrolide antibiotic clarithromycin and the antidepressant nefazodone have been added to the paragraph describing the risk of myopathy with erythromycin. The qualification, "in seriously ill patients", used to describe the cases of rhabdomyolysis associated with concomitant erythromycin has been deleted.
4. A statement advising physicians to interrupt therapy a few days before elective major surgery has been added. It is included as an amendment to the paragraph recommending discontinuation of therapy in patients with myopathy or those predisposed to renal failure secondary to rhabdomyolysis.

PRECAUTIONS, Drug Interactions

The drug interactions with clarithromycin, ketoconazole, and nefazone have been included.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use. Accordingly, the supplemental application is approved effective on the date of this letter.

We will not review the final printed labeling submitted on September 18, 1997 (although it will be retained in our files) because the changes to the WARNINGS and PRECAUTIONS approved in this supplement (S-053) were included in final printed labeling (#7825340) for

supplement-050 submitted January 12, 1998. These changes had not been included in the draft text for supplement-050 that was approved August 12, 1997.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

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

If you have any questions, please contact Margaret Simoneau, R.Ph., Regulatory Management Officer, at (301) 827-6418.

Sincerely yours,

/S/ 1/21/98

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

APPEARS THIS WAY

APPEARS THIS WAY

cc:

Original NDA 19-643

HFD-510/Div. files

HFD-510/CSO/M. Simoneau

HFD-510/D.Orloff/W.Berlin/S.Moore/E.Barbehenn/R.Steigerwalt/E.Galliers

DISTRICT OFFICE

HF-2/Medwatch (with labeling)

HFD-92/DDM-DIAB (with labeling)

HFD-40/DDMAC (with labeling)

HFD-613/OGD (with labeling)

HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.

HFD-560/OTC (with labeling - for OTC Drug Products Only)

HFI-20/Press Office (with labeling)

Drafted by: Mas/April 10, 1998/19643.5

Initialed

by:D.Orloff4.10.98/W.Berlin4.13.98/S.Moore4.13.98/E.Barbehenn4.10.98/R.Steigerwalt
4.10.98/E.Galliers

final:Mas4.20.98

APPROVAL (AP)

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/S/ H/21/98

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019643/S051/S053

FINAL PRINTED LABELING

INAL



7825339

MEVACOR® (Lovastatin)

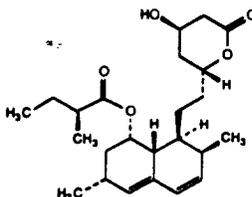
MERCK & CO., INC.
West Point, PA 19486, USA

TABLETS
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 β -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 [1S-[1 α (R*),3 α ,7 β ,8 β (2S*,4S*),8 β]]-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 C₂₄H₃₈O₅ and its molecular weight is 404.55. Its structural formula is:



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

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. 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 Lp(a), fibrinogen, 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 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 lovastatin.

Following an oral dose of ¹⁴C-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 radioc activity (lovastatin plus ¹⁴C-metabolites) peaked at 2 hour and declined rapidly to about 10% of peak by 24 hours post dose. Absorption of lovastatin, estimated relative to an intravenous reference dose, in each of four animal species tested averaged about 30% of an oral dose. In animal studies, after oral dosing, 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 inhibitor. 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 β -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 β -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 dose administration. While the recommended therapeutic dose range is 10 to 80 mg/day, linearity of inhibitor activity in the general circulation was established by a single dose study employing lovastatin tablet dosages from 60 to 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 mixed hyperlipidemia. A marked response was seen within 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 10 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 through IV for dosing results).

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

TABLE I
MEVACOR vs. Placebo
(Mean Percent Change from Baseline After 6 Weeks)

DOSAGE	N	TOTAL-C	LDL-C	HDL-C	LDL-C/HDL-C	TOTAL-C/HDL-C	TRIG.
Placebo	33	-2	-1	-1	0	+1	+9
MEVACOR							
10 mg q.p.m.	33	-16	-21	+5	-24	-19	-10
20 mg q.p.m.	33	-19	-27	+6	-30	-23	+9
10 mg b.i.d.	32	-18	-28	+8	-33	-25	-7
40 mg q.p.m.	33	-22	-31	+5	-33	-25	-8
20 mg b.i.d.	36	-24	-32	+2	-32	-24	-8

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								
20 mg b.i.d.	85	-27	-32	+9	-36	-31	-34	-21
40 mg b.i.d.	86	-34	-42	+8	-44	-37	-31	-27
Cholestyramine								
12 g b.i.d.	86	-17	-23	+8	-27	-21	+2	+11

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7825339 MEVACOR® (Lovastatin)

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

Following an oral dose of ¹⁴C-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 ¹⁴C-metabolites) peaked at 2 hours and declined rapidly to about 10% of peak by 24 hours post-dose. Absorption of lovastatin, estimated relative to an intravenous reference dose, in each of four animal species tested, averaged about 30% of an oral dose. In animal studies, after oral dosing, 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 β-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 β-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 dose administration. While the recommended therapeutic dose range is 10 to 80 mg/day, linearity 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 10 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 through IV for dose response results).

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

TABLE I
MEVACOR vs. Placebo
(Mean Percent Change from Baseline After 8 Weeks)

DOSAGE	N	TOTAL-C	LDL-C	HDL-C	LDL-C/ HDL-C	TOTAL-C/ HDL-C	TRIG.
Placebo	33	-2	-1	-1	0	+1	+8
MEVACOR							
10 mg q.p.m.	33	-16	-21	+5	-24	-19	-10
20 mg q.p.m.	33	-19	-27	+6	-30	-23	+8
10 mg b.i.d.	32	-19	-26	+8	-33	-25	-7
40 mg q.p.m.	33	-22	-31	+5	-33	-25	-8
20 mg b.i.d.	36	-24	-32	+2	-32	-24	-6

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	LDL-C	HDL-C	LDL-C/ HDL-C	TOTAL-C/ HDL-C	VLDL-C	TRIG.
MEVACOR								
20 mg b.i.d.	85	-27	-32	+9	-36	-31	-34	-21
40 mg b.i.d.	88	-34	-42	+8	-44	-37	-31	-27
Cholestyramine								
12 g b.i.d.	88	-17	-23	+8	-27	-21	+2	+11

MEVACOR® (Lovastatin)

TABLE III
MEVACOR vs. Probucol
(Percent Change from Baseline After 14 Weeks)

TREATMENT	N	TOTAL-C	LDL-C	HDL-C	LDL-C/ HDL-C	TOTAL-C/ HDL-C	VLDL-C	TRIG.
MEVACOR								
40 mg q.p.m.	47	-25	-32	+9	-38	-31	-37	-18
80 mg q.p.m.	46	-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

MEVACOR was studied in controlled trials in hypercholesterolemic patients with well-controlled non-insulin dependent diabetes mellitus with normal renal function. The effect of MEVACOR on lipids and lipoproteins and the safety profile of MEVACOR were similar to that demonstrated in studies in nondiabetics. MEVACOR had no clinically important effect on glycemic control or on the dose requirement of oral hypoglycemic agents.

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
(Average Values Between Weeks 12 and 48)

DOSAGE	N**	TOTAL-C	LDL-C	HDL-C	LDL-C/ HDL-C	TOTAL-C/ HDL-C	TRIG.
Placebo	1863	+0.7	+0.4	+2.0	+0.2	+0.6	+4
MEVACOR							
20 mg q.p.m.	1842	-17	-24	+6.6	-27	-21	-10
40 mg q.p.m.	1845	-22	-30	+7.2	-34	-26	-14
20 mg b.i.d.	1846	-24	-34	+8.6	-38	-29	-16
40 mg b.i.d.	1849	-29	-40	+9.5	-44	-34	-19

**Patients enrolled

Atherosclerosis

In the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT), the effect of therapy with lovastatin on coronary atherosclerosis was assessed by coronary angiography in hyperlipidemic patients. In the randomized, double-blind, controlled clinical trial, patients were treated with conventional measures (usually diet and 325 mg of aspirin every other day) and either lovastatin 20-80 mg daily or placebo. Angiograms were evaluated at baseline and at two years by computerized quantitative coronary angiography (QCA). Lovastatin significantly slowed the progression of lesions as measured by the mean change per-patient in minimum lumen diameter (the primary endpoint) and percent diameter stenosis, and decreased the proportions of patients categorized with disease progression (33% vs. 50%) and with new lesions (16% vs. 32%).

In a similarly designed trial, the Monitored Atherosclerosis Regression Study (MARS), patients were treated with diet and either lovastatin 80 mg daily or placebo. No statistically significant difference between lovastatin and placebo was seen for the primary endpoint (mean change per patient in percent diameter stenosis of all lesions), or for most secondary QCA endpoints. Visual assessment by angiographers who formed a consensus opinion of overall angiographic change (Global Change Score) was also a secondary endpoint. By this endpoint, significant slowing of disease was seen, with regression in 23% of patients treated with lovastatin compared to 11% of placebo patients.

In the Familial Atherosclerosis Treatment Study (FATS), either lovastatin or niacin in combination with a bile acid sequestrant for 2.5 years in hyperlipidemic subjects significantly reduced the frequency of progression and increased the frequency of regression of coronary atherosclerotic lesions by QCA compared to diet and, in some cases, low-dose resin.

The effect of lovastatin on the progression of atherosclerosis in the coronary arteries has been corroborated by similar findings in another vasculature. In the Asymptomatic Carotid Artery Progression Study (ACAPS), the effect of therapy with lovastatin on carotid atherosclerosis was assessed by B-mode ultrasonography in hyperlipidemic patients with early carotid lesions and without known coronary heart disease at baseline. In this double-blind, controlled clinical trial, 919 patients were randomized in a 2 x 2 factorial design to placebo, lovastatin 10-40 mg daily and/or warfarin. Ultrasonograms of the carotid walls were used to determine the change per patient from baseline to three years in mean maximum intimal-medial thickness (IMT) of 12 measured segments. There was a significant regression of carotid lesions in patients receiving lovastatin alone compared to those receiving placebo alone (p=0.001). The predictive value of changes in IMT for stroke has not yet been established. In the lovastatin group there was a significant reduction in the number of patients with major cardiovascular events relative to the placebo group (5 vs. 14) and a significant reduction in all-cause mortality (1 vs. 8).

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

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TABLETS
MEVACOR®
(LOVASTATIN)

Circular Number 7825339



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TABLETS
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7825339
MEVACOR® (Lovastatin)

patient, including those with opacities noted at baseline, discontinued from therapy because of a decrease in visual acuity. A three-year, double-blind, placebo-controlled study in hypercholesterolemic patients to assess the effect of lovastatin on the human lens demonstrated that there were no clinically or statistically significant differences between the lovastatin and placebo groups in the incidence, type or progression of lenticular opacities. There are no controlled clinical data assessing the lens available for treatment beyond three years.

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 restricted in saturated fat and cholesterol and to other nonpharmacological measures alone has been inadequate.

MEVACOR is also indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total and LDL cholesterol to target levels.

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, alcoholism) should be excluded, and a lipid profile performed to measure TOTAL-C, HDL-C, and triglycerides (TG). For patients with TG less than 400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation:

$LDL-C = Total\ cholesterol - (0.2 \times (triglycerides) + HDL-C)$
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 National Cholesterol Education Program (NCEP) Treatment Guidelines are summarized below:

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

[†]Coronary heart disease or peripheral vascular disease (including asymptomatic 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; hyperlipidemia; 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 MEVACOR 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).^{***}

CONTRAINDICATIONS

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

Pregnancy and lactation. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR may cause fetal harm when administered to a pregnant woman. Therefore, 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

*****Classification of Hyperlipoproteinemias**

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

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

MEVACOR® (Lovastatin)

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 slowly 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 (see CLINICAL PHARMACOLOGY, Clinical Studies), the incidence of marked persistent increases in serum transaminases over 48 weeks was 0.1% for placebo, 0.1% at 20 mg/day, 0.9% at 40 mg/day, and 1.5% at 80 mg/day in patients on lovastatin. However, in 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 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 MEVACOR 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 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 of normal) 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 transplant patients, and when combined in non-transplant patients with either gemfibrozil or lipid-lowering doses (≥1 g/day) of nicotinic acid. Some of the affected patients had 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.

Myopathy or rhabdomyolysis has occurred in transplant and non-transplant patients receiving MEVACOR or another HMG-CoA reductase inhibitor following the initiation of treatment with the antifungal agents itraconazole and ketoconazole. In a study in normal volunteers, plasma levels of lovastatin were increased about 20-fold when administered concomitantly with itraconazole. This is probably related to metabolism of both drugs by the same P-450 isofor. Based on this data, therapy with MEVACOR should be temporarily interrupted if systemic azole derivative antifungal therapy is required.

Rhabdomyolysis with or without renal impairment has been reported in patients receiving the macrolide antibiotics erythromycin and clarithromycin concomitantly with lovastatin. Rhabdomyolysis has also been reported with the concomitant use of the antidepressant nefazodone and another HMG-CoA reductase inhibitor. Therefore, patients receiving concomitant lovastatin and macrolide antibiotics or nefazodone should be carefully monitored.

Fulminant 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 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 rhabdomyo-

LDL-C (mean) TRIG. (median)
-37 -18
-37 -17
-40 -25
-13 +1

hypercholesterolemia dependent. The effect of safety profiles of studies in effect on oral hypogly-

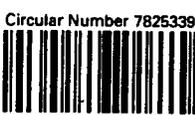
EXCEL Study 3,245 patients 140-300 mg/dL >160 mg/dL (end, parallel, lipid measure- ments were dose- independent (p<0.001). study.

TABLETS
MEVACOR®
(LOVASTATIN)



TOTAL-C/ HDL-C (mean) TRIG. (median)
+0.6 +4
-21 -10
-26 -14
-29 -16
-34 -19

TABLETS
MEVACOR®
(LOVASTATIN)



Intervention Trial coronary ath- erosclerosis in hyper-cholesterolemia, with conven- tional aspirin every 7 or placebo. two years by V (QCA). Lov- astatin as mea- surement of lumen diameter stenosis categorized in new lesions

TABLETS
MEVACOR®
(LOVASTATIN)



hypercholesterolemia with diet and statins. Statins are statistically signif- icant. A study was seen for percent stenosis. Secondary QCA who formed plaques. Global By this end- point regression reduced to 11% of

TABLETS
MEVACOR®
(LOVASTATIN)



study (FATS). In a bile acid study, subjects signif- icantly increased atherosclerotic cases, low-

TABLETS
MEVACOR®
(LOVASTATIN)



atherosclerosis. In a study of similar patients, Carotid artery therapy with lovastatin and B-mode early carotid artery at baseline. Patients were on lovastatin. In the carotid artery patient from the medial-lateral was a signif- icant reduction in stroke risk. There was a major impact (p < 0.05 vs. 14 vs. 8).

TABLETS
MEVACOR®
(LOVASTATIN)



lenticular opacities. In clinical trials, the incidence of new opacities in patients was any



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sis, including: severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures. Also, as there are no known adverse consequences of brief interruption of therapy, treatment with lovastatin should be stopped a few days before elective major surgery.

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) were taking lovastatin concomitantly with immunosuppressive drugs, gemfibrozil or lipid-lowering doses of nicotinic acid. In initial clinical trials, about 30 percent of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy. Most of these patients were receiving lovastatin at doses of 40 to 80 mg/day. In reports from 7 subsequent studies, 148 cyclosporine-treated patients (105 cardiac and 43 renal) received concurrent lovastatin doses of 10 to 60 mg/day (the majority receiving 20 mg/day) for mean periods of 3 to 15 months. There was one case of rhabdomyolysis (0.6%) and one case of significant CPK elevation. In earlier studies of patients taking lovastatin in combination with gemfibrozil or niacin, the incidences of myopathy were approximately 5% and 2%, respectively.

In six 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, Itraconazole, Ketoconazole, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin, Clarithromycin, Nefazodone: See WARNINGS, Skeletal Muscle.

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.

Antipyrene: Lovastatin had no effect on the pharmacokinetics of antipyrene or its metabolites. However, since lovastatin is metabolized by the cytochrome P-450 isoform 3A4, this does not preclude an interaction with other drugs metabolized by the same isoform.

Propranolol: In 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.

Oral Hypoglycemic Agents: In pharmacokinetic studies of MEVACOR in hypercholesterolemic non-insulin dependent diabetic patients, there was no drug interaction with glipizide or with chlorpropamide (see CLINICAL PHARMACOLOGY, Clinical Studies).

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 drug effects on basal and reserve steroid levels. However, clinical studies have shown that lovastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve, and does not reduce basal plasma testosterone concentration. Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG. In the same 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, spironolactone, 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). Vestibulocochlear 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_{max}) 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_{max}) 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.

Cataracts were seen in dogs treated for 11 and 28 weeks at 180 mg/kg/day and 1 year at 60 mg/kg/day.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 21-month carcinogenic 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 total plasma drug exposure 3 to 4 times that of humans given the highest recommended dose of lovastatin (drug exposure was measured as total HMG-CoA reductase inhibitory activity in extracted plasma). Tumor increases were not seen at 20 and 100 mg/kg/day, doses that produced 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 beginning 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 carcinogenicity 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).

An increased incidence of thyroid neoplasms in rats appears to be a response that has been seen with other HMG-CoA reductase inhibitors.

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 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.

APPEARS THIS WAY
ON ORIGINAL

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 or mouse 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.

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 25 mg/kg 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 reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of 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

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/m² surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in either species at multiples of 8 times (rat) or 4 times (mouse) based on surface area. No 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). 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 lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy. 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 pediatric patients have not been established. Because pediatric patients are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of pediatric patients with 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 of up to 14 weeks due to adverse experiences attributable to MEVACOR. About 3% of 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:

	MEVACOR (N = 813) %	Placebo (N = 82) %	Cholestyramine (N = 88) %	Probucol (N = 37) %
Gastrointestinal				
Constipation	4.9	—	34.1	2.1
Diarrhea	5.5	4.9	8.0	10.3
Dyspepsia	3.9	—	13.6	3.1
Flatulence	6.4	2.4	21.6	2.1
Abdominal pain/cramps	5.7	2.4	5.7	5.2
Heartburn	1.6	—	8.0	—
Nausea	4.7	3.7	9.1	6.2
Musculoskeletal				
Muscle cramps	1.1	—	1.1	—
Myalgia	2.4	1.2	—	—
Nervous System/Psychiatric				
Dizziness	2.0	1.2	—	1.0
Headache	9.3	4.9	4.5	8.2
Skin				
Rash/pruritus	5.2	—	4.5	—
Special Senses				
Blurred vision	1.5	—	1.1	3.1
Dysgeusia	0.8	—	1.1	—

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Dyspepsia
Flatulence
Nausea
Musculoskeletal
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Myalgia
Nervous System/
Psychiatric
Dizziness
Headache
Skin
Rash
Special Senses
Blurred vision

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OVERDOSAGE

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Heartburn	1.6	—	8.0	—
Nausea	4.7	3.7	8.1	6.2
Musculoskeletal				
Muscle cramps	1.1	—	1.1	—
Myalgia	2.4	1.2	—	—
Nervous System/Psychiatric				
Dizziness	2.0	1.2	—	1.0
Headache	9.3	4.9	4.5	6.2
Skin				
Rash/pruritus	5.2	—	4.5	—
Special Senses				
Blurred vision	1.5	—	1.1	3.1
Dysgeusia	0.8	—	1.1	—

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, 9 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.

	Placebo (N = 1863) %	MEVACOR 20 mg q.d. (N = 1842) %	MEVACOR 40 mg q.d. (N = 1845) %	MEVACOR 20 mg b.i.d. (N = 1846) %	MEVACOR 40 mg b.i.d. (N = 1848) %
Body As a Whole					
Asthenia	1.4	1.7	1.4	1.5	1.2
Gastrointestinal					
Abdominal pain	1.8	2.0	2.0	2.2	2.5
Constipation	1.9	2.0	3.2	3.7	3.5
Diarrhea	2.3	2.6	2.4	2.2	2.6
Dyspepsia	1.9	1.3	1.3	1.0	1.6
Flatulence	4.2	3.7	4.3	3.9	4.5
Nausea	2.5	1.9	2.5	2.2	2.2
Musculoskeletal					
Muscle cramps	0.5	0.6	0.8	1.1	1.0
Myalgia	1.7	2.8	1.8	2.2	3.0
Nervous System/Psychiatric					
Dizziness	0.7	0.7	1.2	0.5	0.5
Headache	2.7	2.6	2.8	2.1	3.2
Skin					
Rash	0.7	0.8	1.0	1.2	1.3
Special Senses					
Blurred vision	0.8	1.1	0.9	0.9	1.2

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. Not all the effects listed below have necessarily been associated with lovastatin therapy.

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

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, psychic disturbances, anxiety, insomnia, depression.

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

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.

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

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

OVERDOSAGE

After oral administration of MEVACOR to mice the median lethal dose observed was >15 g/m².

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 (see NCEP Treatment Guidelines for details on dietary therapy). MEVACOR should be given with meals.

The usual recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 10-80 mg/day in single or two divided doses; the maximum recommended dose is 80 mg/day. Doses should be individualized according to the recommended goal of therapy (see NCEP Guidelines) and the patient's response (see Tables I to IV under CLINICAL PHARMACOLOGY, Clinical Studies for dose response results). Patients requiring reductions in LDL cholesterol of 20% or more to achieve their goal (see INDICATIONS AND USAGE) should be started on 20 mg/day of MEVACOR. A starting dose of 10 mg may be considered for patients requiring smaller reductions. Adjustments should be made at intervals of 4 weeks or more.

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 significantly 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 on one side and MEVACOR on the other. 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 on one side and MEVACOR on the other. They are supplied as follows:

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

(6505-01-267-2497, 20 mg 60's)

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

(6505-01-267-7925, 20 mg 100's)

NDC 0006-0731-82 bottles of 1000

(6505-01-359-1865, 20 mg 1000's)

NDC 0006-0731-87 bottles of 10,000

(6505-01-379-7905, 20 mg 10,000's).

No. 3562 — Tablets MEVACOR 40 mg are green, octagonal tablets, coded MSD 732 on one side and MEVACOR on the other. They are supplied as follows:

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

(6505-01-310-0615, 40 mg 60's)

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

(6505-01-379-7905, 40 mg 1000's)

(6505-01-379-7903, 40 mg 10,000's).

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.

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

Issued July 1997

Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019643/S051/S053

CHEMISTRY REVIEW(S)

ORIGINAL

MAY 29 1997

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
	DMEDP II, HFD-510	19-643
3. NAME AND ADDRESS OF APPLICANT		4. SUPPLEMENT NUMBER, DATE
Merck Research Labs. PO Box 4, BLA-20 SUMneytown Pike West Point, PA 19486		SCS-051 1-6-97
5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
Tablets Mevacor	Lovastatin	
8. SUPPLEMENT PROVIDES FOR		
The deletion of two raw materials controls from the drug substance manufacturing process, namely,		
9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
antihypercholesteremic	RX	
12. DOSAGE FORM	13. POTENCY	
tablets, oral	10, 20, 40 mg	
14. CHEMICAL NAME AND STRUCTURE		
See Chemistry Review #1		
15. COMMENTS		
<p>For the first item, _____, the sponsor noted that the material is utilized as a _____ . Therefore, the sponsor identifies the assay _____ . A test for "physical characteristics" will be retained for acceptance of this material. Secondly, the sponsor wishes to drop the regulatory method for _____ in favor of the _____ already described in the NDA. The reason for this change is that the original method _____</p>		
16. CONCLUSION AND RECOMMENDATION		
<p>The sponsor has adequately justified _____ and deletion of the original _____ letter. _____ Issue an approval</p>		
17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
WILLIAM K. BERLIN		5-29-97
DISTRIBUTION: ORIGINAL JACKET	CSO	REVIEWER
		DIVISION FILE

5/29/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019643/S051/S053

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date JAN 17 1997

NDA No. 19-643

MERCK RESEARCH LABORATORIES, INC.
West Point, PA 19486

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

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: EVACOR (lovastatin)

NDA Number: 19-643

Supplement Number: S-051

Date of Supplement: January 6, 1997

Date of Receipt: January 10, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on MAR 11 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products
Attention: Document Control Room
5600 Fishers Lane, HFD-510
Rockville, MD 20857

APPROPRIATE
ORIGINAL

Sincerely yours

/S/

Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office Drug Evaluation II
Center for Drug Evaluation and Research

APPROPRIATE
ORIGINAL

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

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ORIGINAL
NDA SUPPLEMENT
Merck & Co.
NDA 19-643
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

19642 REF. NO. 051
NDA SUPPL FOR 505

January 6, 1997



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:

Supplemental New Drug Application: NDA 19-643
MEVACOR™ (Lovastatin)

Pursuant to Section 505(b) of the Food Drug and Cosmetic Act and in accordance with 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)(i) of the approved New Drug Application for MEVACOR™.

The attached supplemental application provides for the removal of two
' from the drug substance section of NDA 19-643 MEVACOR™
tablets. The first revision involves included for the
and the second revision involves

Merck & Co. Inc. wishes to remove the included for
because is a has never
been from where Merck purchases nor by Merck &
Co. Inc. From the literature, one finds that

is the
followed by The remaining is a combination of
other
based on is at a

Therefore, the NDA requirement for

Visual checks

Merck and Co. Inc also wishes
The method, currently outlined in the NDA
we wish

Attachment I includes an electronically annotated and clean copy of the
incorporating the revisions outlined above. Attachment II includes

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

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

REVIEWS COMPLETED	
ACTION:	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I.
<input type="checkbox"/> MEMO	
CSO INITIALS	DATE

Handwritten: 3/6/97

Sincerely,

APPEARS THIS WAY ON ORIGINAL
Robert E. Silverman, M.D., Ph.D.
Director, Regulatory Affairs

Attachments

Desk Copy: Philadelphia District Office
Food and Drug Administration
Room 900
U.S. Custom House
2nd & Chestnut Streets
Philadelphia, Pennsylvania 19106-2973
Certified No. P 914 177 425

APPEARS THIS WAY ON ORIGINAL



Food and Drug Administration
Rockville MD 20857

NDA 19-643/S-053

MERCK RESEARCH LABORATORIES, INC.
Sumneytown Pike
West Point, PA 19486

SEP 26 1997

Attention: Robert E. Silverman, M.D., Ph.D., Senior Director, Regulatory Affairs

Dear Dr. R. E. Silverman:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: MEVACOR (Lovastatin) Tablets

NDA Number: 19-643

Supplement Number: S-053

Date of Supplement: September 18, 1997

Date of Receipt: September 19, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on November 18, 1997, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

RECEIVED
SEP 26 1997
FEDERAL

Sincerely, /S/

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 19-643/S-053

Page 2

cc:

Original NDA 19-643/S-053

HFD-510/Div. Files

HFD-510/CSO/M. Simoneau

filename:

SUPPLEMENT ACKNOWLEDGEMENT

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

These copies are OFFICIAL FDA Copies
not desk copies.

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

NDA No. _____ REF. NO. _____
NDA SUPPLEMENT FOR _____



September 18, 1997

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



APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Sobel:

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

NDA 19-643: MEVACOR™ (Lovastatin)

Pursuant to Section 505(b) of the Food Drug and Cosmetic Act and in accordance with 21 CFR 314.70(c)(2), we submit a supplement to NDA 19-643.

As indicated on the attached Form FDA 356h, the supplemental application provides for changes in Item 4(c)ii of the approved New Drug Application for MEVACOR™.

The circular has been revised under WARNINGS, Skeletal Muscle and PRECAUTIONS, Drug Interactions to include the interactions with the macrolide antibiotic clarithromycin and the antidepressant nefazodone. The qualifications, "in seriously ill patients" and "cardiac transplant patients", used to describe the cases of rhabdomyolysis associated with concomitant erythromycin and immunosuppressant therapy, respectively, have been deleted. As ketoconazole is also a commonly prescribed azole derivative antifungal, it has been included along with the interaction with itraconazole. The recommendation to discontinue therapy in patients with myopathy or those predisposed to renal failure secondary to rhabdomyolysis has been amended to include a statement advising physicians to interrupt therapy a few days before elective major surgery.

APPEARS THIS WAY
ON ORIGINAL

noted
9/24/97

Label accepted

MS/ 9-29-97
4-10-98

Attached for submission are the following:

- Summary of Revisions
- Draft package circular illustrating the revisions.
- Supportive documents including a report (Concomitant Use of Lovastatin with Inhibitors of CYP3A4), references, and appendices.
- Printed Package Circular #7825339 - 15 mounted copies.

The changes will become effective on or about November 1, 1997 and will apply to all packages of MEVACOR™ distributed from the company's manufacturing facilities at West Point, Pennsylvania.

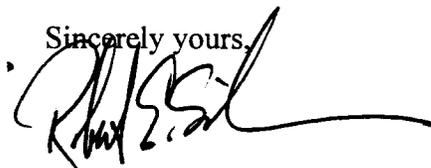
As required by Section 306(k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a (k)(1)], we hereby certify that, in connection with this application, Merck & Co., Inc. did not and will not use in any capacity the services of any person debarred under subsections 306 (a) or (b) of the Act.

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

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

REVIEWS COMPLETED	
CSO ACTION:	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
<i>/S/</i>	<i>h.t. 4-22-97</i>
CSO INITIALS	DATE

Sincerely yours,



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

Attachments

Federal Express

Nov 12 1997
/S/