CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

019643Orig1s085

Trade Name: Mevacor

Generic Name: Lovastatin

Sponsor: Merck & Co., Inc.

Approval Date: 02/28/2012

Indications: to lower total-C and LDL-C to target levels when the response to diet and other nonpharmacological measures alone has been inadequate to reduce risk; to reduce the risk of myocardial infarction; unstable angina; coronary revascularization procedures; to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total-C and LDL-C to target levels; hypercholesterolemia; an adjunct to diet for the reduction of elevated total-C and LDL-C levels in patients with primary hypercholesterolemia (Types IIa and IIb***); adolescent Patients with Heterozygous Familial Hypercholesterolemia; an adjunct to diet to reduce total-C, LDL-C and apolipoprotein B levels in adolescent boys and girls who are at least one year post-menarche, 10-17 years of age, with heFH if after an adequate trial of diet therapy the following findings are present: LDL-C remains >189 mg/dL or
LDL-C remains >160 mg/dL and: there is a positive family history of premature cardiovascular disease or two or more other CVD risk factors are present in the adolescent patient.

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CONTENTS

Reviews / Information Included in this NDA Review.

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

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 19643/S-085

SUPPLEMENT APPROVAL

Merck Sharp & Dohme Corp.
Attention: David R. Hobart, Ph.D.
Manager, Worldwide Regulatory Affairs
P.O. Box 2000, RY 33-208
Rahway NJ 07065-0900

Dear Dr. Hobart:

Please refer to your Supplemental New Drug Application (sNDA) dated October 28, 2011, received October 28, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mevacor (lovastatin) Tablets 20 mg and 40 mg.

We acknowledge receipt of your amendments dated January 13 and 27, and February 3 and 17, 2012.

We also refer to our letter dated August 11, 2011, requesting that sponsors of HMG-CoA reductase inhibitor (statin) drugs, modify their labeling based on our comprehensive review of clinical trial data, Adverse Event Reporting System (AERS) reports, the published literature, and the labels of other approved drugs containing information on statin coadministration.

This "Prior Approval" supplemental new drug application provides for revisions to the **CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION** sections of the Mevacor (lovastatin) package insert.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Margaret Simoneau, M.S., R.Ph., Regulatory Project Manager, at (301) 796-1295.

Sincerely,

{See appended electronic signature page}

Amy G. Egan, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY G EGAN
02/28/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019643Orig1s085

LABELING

Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

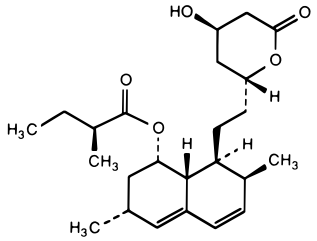
TABLETS

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 [1*S*-[1α(*R**),3α,7β,8β(2*S**,4*S**), 8aβ]]-1,2,3,7, 8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate. The empirical formula of lovastatin is $C_{24}H_{36}O_5$ 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 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 20 mg also contain FD&C Blue 2 aluminum lake. Tablets MEVACOR 40 mg also contain D&C Yellow 10 aluminum lake and FD&C Blue 2 aluminum lake.

CLINICAL PHARMACOLOGY

The involvement of low-density lipoprotein cholesterol (LDL-C) in atherogenesis has been well-documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological and clinical studies have established that high LDL-C and low high-density lipoprotein cholesterol (HDL-C) are both associated with coronary heart disease. However, the risk of developing coronary heart disease is continuous and graded over the range of cholesterol levels and many coronary events do occur in patients with total cholesterol (total-C) and LDL-C in the lower end of this range.

MEVACOR has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very low-density lipoprotein (VLDL) and is catabolized predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of MEVACOR may involve both reduction of VLDL-C concentration, and induction of the LDL receptor, leading to reduced production and/or increased catabolism of LDL-C. 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-C, and modestly reduces VLDL-C and plasma

triglycerides (TG) (see Tables II-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 strong 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 ^{14}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 ^{14}C-metabolites) peaked at 2 hours and declined rapidly to about 10% of peak by 24 hours postdose. 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.

In a study including 16 elderly patients between 70-78 years of age who received MEVACOR 80 mg/day, the mean plasma level of HMG-CoA reductase inhibitory activity was increased approximately 45% compared with 18 patients between 18-30 years of age (see PRECAUTIONS, *Geriatric Use*).

Although the mechanism is not fully understood, cyclosporine has been shown to increase the AUC of HMG-CoA reductase inhibitors. The increase in AUC for lovastatin and lovastatin acid is presumably due, in part, to inhibition of CYP3A4.

The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Strong inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*).

Lovastatin is a substrate for cytochrome P450 isoform 3A4 (CYP3A4) (see PRECAUTIONS, *Drug Interactions*). Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase

the plasma concentrations of drugs metabolized by CYP3A4. In one study**, 10 subjects consumed 200 mL of double-strength grapefruit juice (one can of frozen concentrate diluted with one rather than 3 cans of water) three times daily for 2 days and an additional 200 mL double-strength grapefruit juice together with and 30 and 90 minutes following a single dose of 80 mg lovastatin on the third day. This regimen of grapefruit juice resulted in a mean increase in the serum concentration of lovastatin and its β-hydroxyacid metabolite (as measured by the area under the concentration-time curve) of 15-fold and 5-fold, respectively [as measured using a chemical assay — high performance liquid chromatography]. In a second study, 15 subjects consumed one 8 oz glass of single-strength grapefruit juice (one can of frozen concentrate diluted with 3 cans of water) with breakfast for 3 consecutive days and a single dose of 40 mg lovastatin in the evening of the third day. This regimen of grapefruit juice resulted in a mean increase in the plasma concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [using an enzyme inhibition assay both before (for active inhibitors) and after (for total inhibitors) base hydrolysis] of 1.34-fold and 1.36-fold, respectively, and of lovastatin and its β-hydroxyacid metabolite [measured using a chemical assay — liquid chromatography/tandem mass spectrometry — different from that used in the first** study] of 1.94-fold and 1.57-fold, respectively. The effect of amounts of grapefruit juice between those used in these two studies on lovastatin pharmacokinetics has not been studied.

TABLE I
The Effect of Other Drugs on Lovastatin Exposure When Both Were Co-administered

	Number of Subjects	**Dosing of Coadministered Drug or Grapefruit Juice**	**Dosing of Lovastatin**	**AUC Ratio* (with / without coadministered drug) No Effect = 1.00**	
				Lovastatin	**Lovastatin acid†**
Gemfibrozil	11	600 mg BID for 3 days	40 mg	0.96	2.80
Itraconazole‡	12	200 mg QD for 4 days	40 mg on Day 4	> 36§	22
	10	100 mg QD for 4 days	40 mg on Day 4	> 14.8§	15.4
Grapefruit Juice¶ (high dose)	10	200 mL of double-strength TID#	80 mg single dose	15.3	5.0
Grapefruit Juice¶ (low dose)	16	8 oz (about 250 mL) of single-strengthÞ for 4 days	40 mg single dose	1.94	1.57
Cyclosporine	16	Not describedß	10 mg QD for 10 days	5- to 8-fold	NDà
	Number of Subjects	**Dosing of Coadministered Drug or Grapefruit Juice**	**Dosing of Lovastatin**	**AUC Ratio* (with / without coadministered drug) No Effect = 1.00**	
				Total Lovastatin acidè	
Diltiazem	10	120 mg BID for 14 days	20 mg	3.57è	

* Results based on a chemical assay.

† Lovastatin acid refers to the β-hydroxyacid of lovastatin.

‡ The mean total AUC of lovastatin without itraconazole phase could not be determined accurately. Results could be representative of strong CYP3A4 inhibitors such as ketoconazole, posaconazole, clarithromycin, telithromycin, HIV protease inhibitors, and nefazodone.

§ Estimated minimum change.

¶ The effect of amounts of grapefruit juice between those used in these two studies on lovastatin pharmacokinetics has not been studied.

Double-strength: one can of frozen concentrate diluted with one can of water. Grapefruit juice was administered TID for 2 days, and 200 mL together with single dose lovastatin and 30 and 90 minutes following single dose lovastatin on Day 3.

Þ Single-strength: one can of frozen concentrate diluted with 3 cans of water. Grapefruit juice was administered with breakfast for 3 days, and lovastatin was administered in the evening on Day 3.

ß Cyclosporine-treated patients with psoriasis or post kidney or heart transplant patients with stable graft function, transplanted at least 9 months prior to study.

à ND = Analyte not determined.

** Kantola, T, et al., Clin Pharmacol Ther 1998; 63(4):397-402.

è Lactone converted to acid by hydrolysis prior to analysis. Figure represents total unmetabolized acid and lactone.

Clinical Studies in Adults

MEVACOR has been shown to be highly effective in reducing total-C and LDL-C 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 plasma total-C, LDL-C, total-C/HDL-C ratio and LDL-C/HDL-C ratio. In addition, MEVACOR produced increases of variable magnitude in HDL-C, and modestly decreased VLDL-C and plasma TG (see Tables II through IV for dose response results).

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

TABLE II
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	TG.
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	–19	–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	–6

MEVACOR was compared to cholestyramine in a randomized open parallel study. The study was performed with patients with hypercholesterolemia who were at high risk of myocardial infarction. Summary results are presented in Table III.

TABLE III
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)	TG. (mean)
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 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-C 240-300 mg/dL [6.2 mmol/L - 7.6 mmol/L], LDL-C >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 ($p \leq 0.001$). 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)	TG. (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.	1645	–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

Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)

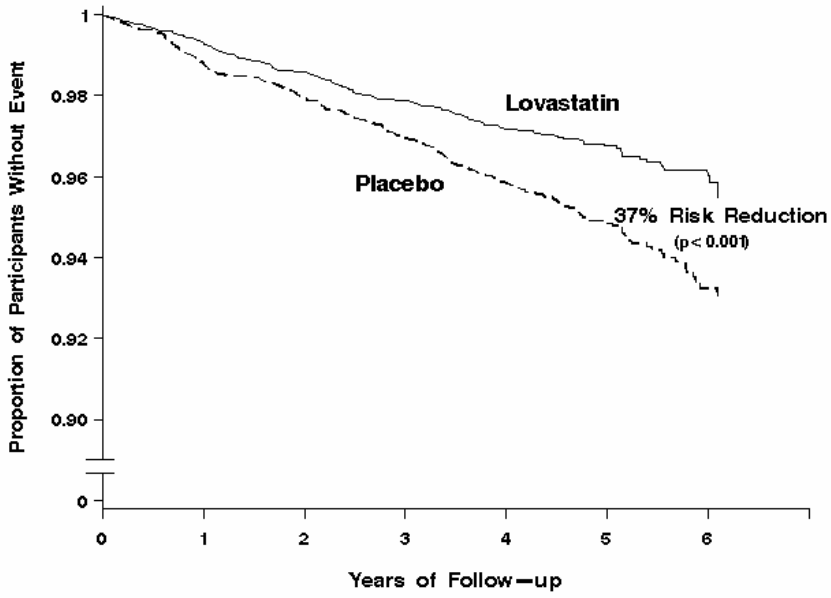
The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), a double-blind, randomized, placebo-controlled, primary prevention study, demonstrated that treatment with MEVACOR decreased the rate of acute major coronary events (composite endpoint of myocardial infarction, unstable angina, and sudden cardiac death) compared with placebo during a median of 5.1 years of follow-up. Participants were middle-aged and elderly men (ages 45-73) and women (ages 55-73) without symptomatic cardiovascular disease with average to moderately elevated total-C and LDL-C, below average HDL-C, and who were at high risk based on elevated total-C/HDL-C. In addition to age, 63% of the participants had at least one other risk factor (baseline HDL-C <35 mg/dL, hypertension, family history, smoking and diabetes).

AFCAPS/TexCAPS enrolled 6,605 participants (5,608 men, 997 women) based on the following lipid entry criteria: total-C range of 180-264 mg/dL, LDL-C range of 130-190 mg/dL, HDL-C of ≤45 mg/dL for men and ≤47 mg/dL for women, and TG of ≤400 mg/dL. Participants were treated with standard care, including diet, and either MEVACOR 20-40 mg daily (n= 3,304) or placebo (n= 3,301). Approximately 50% of the participants treated with MEVACOR were titrated to 40 mg daily when their LDL-C remained >110 mg/dL at the 20-mg starting dose.

MEVACOR reduced the risk of a first acute major coronary event, the primary efficacy endpoint, by 37% (MEVACOR 3.5%, placebo 5.5%; p<0.001; Figure 1). A first acute major coronary event was defined as myocardial infarction (54 participants on MEVACOR, 94 on placebo) or unstable angina (54 vs. 80) or sudden cardiac death (8 vs. 9). Furthermore, among the secondary endpoints, MEVACOR reduced the risk of unstable angina by 32% (1.8 vs. 2.6%; p=0.023), of myocardial infarction by 40% (1.7 vs. 2.9%; p=0.002), and of undergoing coronary revascularization procedures (e.g., coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 33% (3.2 vs. 4.8%; p=0.001). Trends in risk reduction associated with treatment with MEVACOR were consistent across men and women, smokers and non-smokers, hypertensives and non-hypertensives, and older and younger participants. Participants with ≥2 risk factors had risk reductions (RR) in both acute major coronary events (RR 43%) and coronary revascularization procedures (RR 37%). Because there were too few events among those participants with age as their only risk factor in this study, the effect of MEVACOR on outcomes could not be adequately assessed in this subgroup.

Figure 1

Acute Major Coronary Events
(Primary Endpoint)



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 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.

Clinical Studies in Adolescent Patients

Efficacy of Lovastatin in Adolescent Boys with Heterozygous Familial Hypercholesterolemia

In a double-blind, placebo-controlled study, 132 boys 10-17 years of age (mean age 12.7 yrs) with heterozygous familial hypercholesterolemia (heFH) were randomized to lovastatin (n=67) or placebo (n=65) for 48 weeks. Inclusion in the study required a baseline LDL-C level between 189 and 500 mg/dL and at least one parent with an LDL-C level >189 mg/dL. The mean baseline LDL-C value was 253.1 mg/dL (range: 171-379 mg/dL) in the MEVACOR group compared to 248.2 mg/dL (range: 158.5-413.5 mg/dL) in the placebo group. The dosage of lovastatin (once daily in the evening) was 10 mg for the first 8 weeks, 20 mg for the second 8 weeks, and 40 mg thereafter.

MEVACOR significantly decreased plasma levels of total-C, LDL-C and apolipoprotein B (see Table V).

TABLE V
Lipid-lowering Effects of Lovastatin in Adolescent Boys with Heterozygous Familial Hypercholesterolemia
(Mean Percent Change from Baseline at Week 48 in Intention-to-Treat Population)

DOSAGE	N	TOTAL-C	LDL-C	HDL-C	TG.*	Apolipoprotein B
Placebo	61	-1.1	-1.4	-2.2	-1.4	-4.4
MEVACOR	64	-19.3	-24.2	+1.1	-1.9	-21

*data presented as median percent changes

The mean achieved LDL-C value was 190.9 mg/dL (range: 108-336 mg/dL) in the MEVACOR group compared to 244.8 mg/dL (range: 135-404 mg/dL) in the placebo group.

Efficacy of Lovastatin in Post-Menarchal Girls with Heterozygous Familial Hypercholesterolemia

In a double-blind, placebo-controlled study, 54 girls 10-17 years of age who were at least 1 year post-menarche with heFH were randomized to lovastatin (n=35) or placebo (n=19) for 24 weeks. Inclusion in the study required a baseline LDL-C level of 160-400 mg/dL and a parental history of familial hypercholesterolemia. The mean baseline LDL-C value was 218.3 mg/dL (range: 136.3-363.7 mg/dL) in the MEVACOR group compared to 198.8 mg/dL (range: 151.1-283.1 mg/dL) in the placebo group. The dosage of lovastatin (once daily in the evening) was 20 mg for the first 4 weeks, and 40 mg thereafter.

MEVACOR significantly decreased plasma levels of total-C, LDL-C, and apolipoprotein B (see Table VI).

TABLE VI
Lipid-lowering Effects of Lovastatin in Post-Menarchal Girls with Heterozygous Familial Hypercholesterolemia
(Mean Percent Change from Baseline at Week 24 in Intention-to-Treat Population)

DOSAGE	N	TOTAL-C	LDL-C	HDL-C	TG.*	Apolipoprotein B
Placebo	18	+3.6	+2.5	+4.8	-3.0	+6.4
MEVACOR	35	-22.4	-29.2	+2.4	-22.7	-24.4

*data presented as median percent changes

The mean achieved LDL-C value was 154.5 mg/dL (range: 82-286 mg/dL) in the MEVACOR group compared to 203.5 mg/dL (range: 135-304 mg/dL) in the placebo group.

The safety and efficacy of doses above 40 mg daily have not been studied in children. The long-term efficacy of lovastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

INDICATIONS AND USAGE

Therapy with MEVACOR should be a component of multiple risk factor intervention in those individuals with dyslipidemia at risk for atherosclerotic vascular disease. MEVACOR should be used in addition to a diet restricted in saturated fat and cholesterol as part of a treatment strategy to lower total-C and LDL-C to target levels when the response to diet and other nonpharmacological measures alone has been inadequate to reduce risk.

Primary Prevention of Coronary Heart Disease

In individuals without symptomatic cardiovascular disease, average to moderately elevated total-C and LDL-C, and below average HDL-C, MEVACOR is indicated to reduce the risk of:

- Myocardial infarction
- Unstable angina
- Coronary revascularization procedures

(See CLINICAL PHARMACOLOGY, *Clinical Studies*.)

Coronary Heart Disease

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

Hypercholesterolemia

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-C and LDL-C 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.

Adolescent Patients with Heterozygous Familial Hypercholesterolemia

MEVACOR is indicated as an adjunct to diet to reduce total-C, LDL-C and apolipoprotein B levels in adolescent boys and girls who are at least one year post-menarche, 10-17 years of age, with heFH if after an adequate trial of diet therapy the following findings are present:

*** Classification of Hyperlipoproteinemias

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

IDL = intermediate-density lipoprotein.

1. LDL-C remains >189 mg/dL or
2. LDL-C remains >160 mg/dL and:
   - there is a positive family history of premature cardiovascular disease or
   - two or more other CVD risk factors are present in the adolescent patient

General Recommendations

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 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-C – [0.2 × (TG) + 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:

NCEP Treatment Guidelines:
LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes
and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD† or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)††
2+ Risk factors (10 year risk ≤20%)	<130	≥130	10-year risk 10-20%: ≥130 10-year risk <10%: ≥ 160
0-1 Risk factor†††	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

† CHD, coronary heart disease

†† Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

††† Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dL, non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C is ≥130 mg/dL (see NCEP Guidelines above).

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-C levels in patients with combined hypercholesterolemia and hypertriglyceridemia where hypercholesterolemia is the major abnormality (Type IIb hyperlipoproteinemia), it has not been studied in conditions where the major abnormality is elevation of chylomicrons, VLDL or IDL (i.e., hyperlipoproteinemia types I, III, IV, or V).***

The NCEP classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature cardiovascular disease is summarized below:

Category	Total-C (mg/dL)	LDL-C (mg/dL)
Acceptable	<170	<110
Borderline	170-199	110-129
High	≥200	≥130

Children treated with lovastatin in adolescence should be re-evaluated in adulthood and appropriate changes made to their cholesterol-lowering regimen to achieve adult goals for LDL-C.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

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

Concomitant administration with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone) (see WARNINGS, *Myopathy/Rhabdomyolysis)*.

Pregnancy and lactation (see PRECAUTIONS, *Pregnancy* and *Nursing Mothers*). 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 is contraindicated during pregnancy and in nursing mothers. **MEVACOR 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, MEVACOR should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see PRECAUTIONS, *Pregnancy*).

WARNINGS

Myopathy/Rhabdomyolysis

Lovastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related. In a clinical study (EXCEL) in which patients were carefully monitored and some interacting drugs were excluded, there was one case of myopathy among 4933 patients randomized to lovastatin 20-40 mg daily for 48 weeks, and 4 among 1649 patients randomized to 80 mg daily.

All patients starting therapy with lovastatin, or whose dose of lovastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Lovastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. In most cases, muscle symptoms and CK increases resolved when treatment was promptly discontinued. Periodic CK determinations may be considered in patients starting therapy with lovastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

Many of the patients who have developed rhabdomyolysis on therapy with lovastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. MEVACOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. MEVACOR therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.

The risk of myopathy/rhabdomyolysis is increased by concomitant use of lovastatin with the following:

Strong inhibitors of CYP3A4: Lovastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of cytochrome P450 3A4 (CYP3A4). Certain drugs which inhibit this metabolic pathway can

raise the plasma levels of lovastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, and posaconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, boceprevir, telaprevir, or the antidepressant nefazodone. Combination of these drugs with lovastatin is contraindicated. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with lovastatin should be suspended during the course of treatment (see CONTRAINDICATIONS; PRECAUTIONS, *Drug Interactions*).

Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentration of lovastatin. It is recommended that dose adjustment of lovastatin be considered during coadministration. Increased lovastatin concentration in plasma has been associated with an increased risk of myopathy/rhabdomyolysis.

Gemfibrozil: The combined use of lovastatin with gemfibrozil should be avoided.

Other lipid-lowering drugs (other fibrates or ≥1 g/day of niacin): Caution should be used when prescribing other fibrates or lipid-lowering doses (≥1 g/day) of niacin with lovastatin, as these agents can cause myopathy when given alone. **The benefit of further alterations in lipid levels by the combined use of lovastatin with other fibrates or niacin should be carefully weighed against the potential risks of these combinations.**

Cyclosporine: The use of lovastatin with cyclosporine should be avoided.

Danazol, diltiazem or verapamil with higher doses of lovastatin: The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with danazol, diltiazem, or verapamil. The benefits of the use of lovastatin in patients receiving danazol, diltiazem, or verapamil should be carefully weighed against the risks of these combinations.

Amiodarone: The dose of lovastatin should not exceed 40 mg daily in patients receiving concomitant medication with amiodarone. The combined use of lovastatin at doses higher than 40 mg daily with amiodarone should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy. The risk of myopathy/rhabdomyolysis is increased when amiodarone is used concomitantly with higher doses of a closely related member of the HMG-CoA reductase inhibitor class.

Colchicine: Cases of myopathy, including rhabdomyolysis, have been reported with lovastatin coadministered with colchicine, and caution should be exercised when prescribing lovastatin with colchicine (see PRECAUTIONS, *Drug Interactions*).

Ranolazine: The risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of ranolazine. Dose adjustment of lovastatin may be considered during co-administration with ranolazine.

Prescribing recommendations for interacting agents are summarized in Table VII (see also CLINICAL PHARMACOLOGY, *Pharmacokinetics*; PRECAUTIONS, *Drug Interactions*; DOSAGE AND ADMINISTRATION).

Table VII
Drug Interactions Associated with Increased
Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Strong CYP3A4 inhibitors, e.g.: Ketoconazole Itraconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Boceprevir Telaprevir Nefazodone	Contraindicated with lovastatin
Gemfibrozil Cyclosporine	Avoid with lovastatin
Danazol Diltiazem Verapamil	Do not exceed 20 mg lovastatin daily
Amiodarone	Do not exceed 40 mg lovastatin daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

Liver Dysfunction

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 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).

In AFCAPS/TexCAPS, the number of participants with consecutive elevations of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (> 3 times the upper limit of normal), over a median of 5.1 years of follow-up, was not significantly different between the MEVACOR and placebo groups (18 [0.6%] vs. 11 [0.3%]). The starting dose of MEVACOR was 20 mg/day; 50% of the MEVACOR treated participants were titrated to 40 mg/day at Week 18. Of the 18 participants on MEVACOR with consecutive elevations of either ALT or AST, 11 (0.7%) elevations occurred in participants taking 20 mg/day, while 7 (0.4%) elevations occurred in participants titrated to 40 mg/day. Elevated transaminases resulted in discontinuation of 6 (0.2%) participants from therapy in the MEVACOR group (n=3,304) and 4 (0.1%) in the placebo group (n=3,301).

It is recommended that liver enzyme tests be obtained prior to initiating therapy with MEVACOR and repeated as clinically indicated.

There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including lovastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with MEVACOR, promptly interrupt therapy. If an alternate etiology is not found do not restart MEVACOR.

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.

PRECAUTIONS

General

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 about substances they should not take concomitantly with lovastatin and be advised to report promptly unexplained muscle pain, tenderness, or weakness (see list below and WARNINGS, *Myopathy/Rhabdomyolysis*). Patients should also be advised to inform other physicians prescribing a new medication that they are taking MEVACOR.

It is recommended that liver enzymes be checked before starting therapy, and if signs or symptoms of liver injury occur. All patients treated with MEVACOR should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.

Drug Interactions

CYP3A4 Interactions

Lovastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Strong inhibitors of CYP3A4 (e.g., itraconazole, ketoconazole, posaconazole, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone, and erythromycin), and large quantities of grapefruit juice (>1 quart daily) increase the risk of myopathy by reducing the elimination of lovastatin. **(See CONTRAINDICATIONS, WARNINGS, *Myopathy/Rhabdomyolysis*, and CLINICAL PHARMACOLOGY, *Pharmacokinetics.*)**

In vitro studies have demonstrated that voriconazole inhibits the metabolism of lovastatin. Adjustment of the lovastatin dose may be needed to reduce the risk of myopathy, including rhabdomyolysis, if voriconazole must be used concomitantly with lovastatin.

Interactions With Lipid-Lowering Drugs That Can Cause Myopathy When Given Alone

The risk of myopathy is also increased by the following lipid-lowering drugs that are not strong CYP3A4 inhibitors, but which can cause myopathy when given alone.

See WARNINGS, *Myopathy/Rhabdomyolysis.*
Gemfibrozil
Other fibrates
Niacin (nicotinic acid) (≥1 g/day)

Other Drug Interactions

Cyclosporine: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine (see WARNINGS, *Myopathy/Rhabdomyolysis*).

Danazol, Diltiazem, or Verapamil: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of danazol, diltiazem, or verapamil particularly with higher doses of lovastatin (see WARNINGS, *Myopathy/Rhabdomyolysis*; CLINICAL PHARMACOLOGY, *Pharmacokinetics*).

Amiodarone: The risk of myopathy/rhabdomyolysis is increased when amiodarone is used concomitantly with a closely related member of the HMG-CoA reductase inhibitor class (see WARNINGS, *Myopathy/Rhabdomyolysis*).

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-second 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.

Colchicine: Cases of myopathy, including rhabdomyolysis, have been reported with lovastatin coadministered with colchicine. See WARNINGS, *Myopathy/Rhabdomyolysis.*

Ranolazine: The risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of ranolazine. See WARNINGS, *Myopathy/Rhabdomyolysis*.

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*).

Endocrine Function

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including MEVACOR.

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 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., 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.

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 in offspring of pregnant mice and rats dosed during gestation at 80 mg/kg/day (affected mouse fetuses/total: 8/307 compared to 4/289 in the control group; affected rat fetuses/total: 6/324 compared to 2/308 in the control group). Female rats dosed before mating through gestation at 80 mg/kg/day also had fetuses with skeletal malformations (affected fetuses/total: 1/152 compared to 0/171 in the control group). The 80 mg/kg/day dose in mice is 7 times the human dose based on body surface area and in rats results in 5 times the human exposure based on AUC. In pregnant rats given doses of 2, 20, or 200 mg/kg/day and treated through lactation, the following effects were observed: neonatal mortality (4.1%, 3.5%, and 46%, respectively, compared to 0.6% in the control group), decreased pup body weights throughout lactation (up to 5%, 8%, and 38%, respectively, below control), supernumerary ribs in dead pups (affected fetuses/total: 0/7, 1/17, and

11/79, respectively, compared to 0/5 in the control group), delays in ossification in dead pups (affected fetuses/total: 0/7, 0/17, and 1/79, respectively, compared to 0/5 in the control group) and delays in pup development (delays in the appearance of an auditory startle response at 200 mg/kg/day and free-fall righting reflexes at 20 and 200 mg/kg/day).

Direct dosing of neonatal rats by subcutaneous injection with 10 mg/kg/day of the open hydroxyacid form of lovastatin resulted in delayed passive avoidance learning in female rats (mean of 8.3 trials to criterion, compared to 7.3 and 6.4 in untreated and vehicle-treated controls; no effects on retention 1 week later) at exposures 4 times the human systemic exposure at 80 mg/day based on AUC. No effect was seen in male rats. No evidence of malformations was observed when pregnant rabbits were given 5 mg/kg/day (doses equivalent to a human dose of 80 mg/day based on body surface area) or a maternally toxic dose of 15 mg/kg/day (3 times the human dose of 80 mg/day based on body surface area).

Rare clinical reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. However, in an analysis[†] of greater than 200 prospectively followed pregnancies exposed during the first trimester to MEVACOR or another closely related HMG-CoA reductase inhibitor, the incidence of congenital anomalies was comparable to that seen in the general population. This number of pregnancies was sufficient to exclude a 3-fold or greater increase in congenital anomalies over the background incidence.

Maternal treatment with MEVACOR may reduce the fetal levels of mevalonate, which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering drugs during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolemia. For these reasons, MEVACOR should not be used in women who are pregnant, or can become pregnant (see CONTRAINDICATIONS). 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. Treatment should be immediately discontinued as soon as pregnancy is recognized.

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 patients 10-17 years of age with heFH have been evaluated in controlled clinical trials of 48 weeks duration in adolescent boys and controlled clinical trials of 24 weeks duration in girls who were at least 1 year post-menarche. Patients treated with lovastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses greater than 40 mg have not been studied in this population**. In these limited controlled studies, there was no detectable effect on growth or sexual maturation in the adolescent boys or on menstrual cycle length in girls. See CLINICAL PHARMACOLOGY, *Clinical Studies in Adolescent Patients*; ADVERSE REACTIONS, *Adolescent Patients*; and DOSAGE AND ADMINISTRATION, *Adolescent Patients (10-17 years of age) with Heterozygous Familial Hypercholesterolemia*. Adolescent females should be counseled on appropriate contraceptive methods while on lovastatin therapy (see CONTRAINDICATIONS and PRECAUTIONS, *Pregnancy*). **Lovastatin has not been studied in pre-pubertal patients or patients younger than 10 years of age.**

Geriatric Use

A pharmacokinetic study with lovastatin showed the mean plasma level of HMG-CoA reductase inhibitory activity to be approximately 45% higher in elderly patients between 70-78 years of age compared with patients between 18-30 years of age; however, clinical study experience in the elderly indicates that dosage adjustment based on this age-related pharmacokinetic difference is not needed. In the two large clinical studies conducted with lovastatin (EXCEL and AFCAPS/TexCAPS), 21% (3094/14850) of patients were ≥65 years of age. Lipid-lowering efficacy with lovastatin was at least as great in elderly patients compared with younger patients, and there were no overall differences in safety over the 20 to 80 mg/day dosage range (see CLINICAL PHARMACOLOGY).

[†] Manson, J.M., Freyssinges, C., Ducrocq, M.B., Stephenson, W.P., Postmarketing Surveillance of Lovastatin and Simvastatin Exposure During Pregnancy. *Reproductive Toxicology*. 10(6):439-446. 1996.

ADVERSE REACTIONS

MEVACOR is generally well tolerated; adverse reactions usually have been mild and transient.

Phase III Clinical Studies

In Phase III controlled clinical studies involving 613 patients treated with MEVACOR, the adverse experience profile was similar to that shown below for the 8,245-patient EXCEL study (see *Expanded Clinical Evaluation of Lovastatin [EXCEL] Study*).

Persistent increases of serum transaminases have been noted (see WARNINGS, *Liver Dysfunction*). About 11% of patients had elevations of CK levels of at least twice the normal value on one or more occasions. The corresponding values for the control agent cholestyramine was 9 percent. This was attributable to the noncardiac fraction of CK. Large increases in CK have sometimes been reported (see WARNINGS, *Myopathy/Rhabdomyolysis*).

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study

MEVACOR was compared to placebo in 8,245 patients with hypercholesterolemia (total-C 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 = 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) %
Body As a Whole					
Asthenia	1.4	1.7	1.4	1.5	1.2
Gastrointestinal					
Abdominal pain	1.6	2.0	2.0	2.2	2.5
Constipation	1.9	2.0	3.2	3.2	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	2.6	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.

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%.

Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)

In AFCAPS/TexCAPS (see CLINICAL PHARMACOLOGY, *Clinical Studies*) involving 6,605 participants treated with 20-40 mg/day of MEVACOR (n=3,304) or placebo (n=3,301), the safety and tolerability profile of the group treated with MEVACOR was comparable to that of the group treated with placebo during a median of 5.1 years of follow-up. The adverse experiences reported in

AFCAPS/TexCAPS were similar to those reported in EXCEL (see ADVERSE REACTIONS, *Expanded Clinical Evaluation of Lovastatin (EXCEL) Study*).

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 gemfibrozil to therapy with lovastatin is not associated with greater reduction in LDL-C than that achieved with lovastatin alone. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with cyclosporine, gemfibrozil or niacin (nicotinic acid). The combined use of lovastatin with cyclosporine or gemfibrozil should be avoided. Caution should be used when prescribing other fibrates or lipid-lowering doses (≥1 g/day) of niacin with lovastatin (see WARNINGS, *Myopathy/Rhabdomyolysis*).

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, arthralgias.

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

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, dermatomyositis, 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, fatal and non-fatal hepatic failure.

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

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

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

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

Adolescent Patients (ages 10-17 years)

In a 48-week controlled study in adolescent boys with heFH (n=132) and a 24-week controlled study in girls who were at least 1 year post-menarche with heFH (n=54), the safety and tolerability profile of the groups treated with MEVACOR (10 to 40 mg daily) was generally similar to that of the groups treated with placebo (see CLINICAL PHARMACOLOGY, *Clinical Studies in Adolescent Patients* and PRECAUTIONS, *Pediatric Use*).

OVERDOSAGE

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

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.

DOSAGE 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.

Adult Patients

The usual recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range of lovastatin 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 CLINICAL PHARMACOLOGY). Patients requiring reductions in LDL-C 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 of lovastatin may be considered for patients requiring smaller reductions. Adjustments should be made at intervals of 4 weeks or more. The 10 mg dosage is provided for information purposes only. Although lovastatin tablets 10 mg are available in the marketplace, MEVACOR is no longer marketed in the 10 mg strength.

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.

Dosage in Patients taking Danazol, Diltiazem, or Verapamil

In patients taking danazol, diltiazem, or verapamil concomitantly with lovastatin, therapy should begin with 10 mg of lovastatin and should not exceed 20 mg/day (see CLINICAL PHARMACOLOGY, *Pharmacokinetics,* WARNINGS, *Myopathy/Rhabdomyolysis*, PRECAUTIONS, *Drug Interactions, Other Drug Interactions*).

Dosage in Patients taking Amiodarone

In patients taking amiodarone concomitantly with MEVACOR, the dose should not exceed 40 mg/day (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*, *Other Drug Interactions*).

Adolescent Patients (10-17 years of age) with Heterozygous Familial Hypercholesterolemia

The recommended dosing range of lovastatin is 10-40 mg/day; the maximum recommended dose is 40 mg/day. Doses should be individualized according to the recommended goal of therapy (see NCEP Pediatric Panel Guidelines[††], CLINICAL PHARMACOLOGY, and INDICATIONS AND USAGE). Patients requiring reductions in LDL-C of 20% or more to achieve their goal should be started on 20 mg/day of MEVACOR. A starting dose of 10 mg of lovastatin may be considered for patients requiring smaller reductions. Adjustments should be made at intervals of 4 weeks or more.

Concomitant Lipid-Lowering Therapy

MEVACOR is effective alone or when used concomitantly with bile-acid sequestrants (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*).

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, *Myopathy/Rhabdomyolysis*).

HOW SUPPLIED

No. 8123 — Tablets MEVACOR 20 mg are blue, octagonal tablets, coded MSD 731 on one side and plain on the other. They are supplied as follows:

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

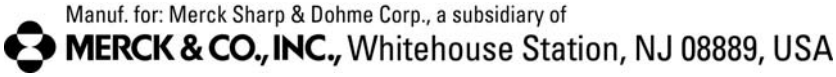
No. 8124 — Tablets MEVACOR 40 mg are green, octagonal tablets, coded MSD 732 on one side and plain on the other. They are supplied as follows:

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

[††] National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics*. 89(3):495-501. 1992.

Storage

Store at 20-25°C (68-77°F). [See USP Controlled Room Temperature.] Tablets MEVACOR must be protected from light and stored in a well-closed, light-resistant container.



By:
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Revised: 02/2012

9844662

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019643Orig1s085

Tracked Changes Label

Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

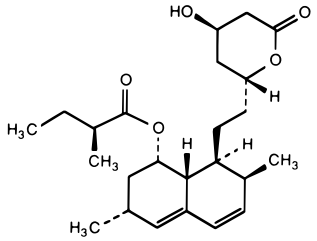
~~9844661~~9844662
~~014-874-01~~

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 [1*S*-[1α(*R**),3α,7β,8β(2*S**,4*S**), 8aβ]]-1,2,3,7, 8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate. The empirical formula of lovastatin is $C_{24}H_{36}O_5$ 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 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 20 mg also contain FD&C Blue 2 aluminum lake. Tablets MEVACOR 40 mg also contain D&C Yellow 10 aluminum lake and FD&C Blue 2 aluminum lake.

CLINICAL PHARMACOLOGY

The involvement of low-density lipoprotein cholesterol (LDL-C) in atherogenesis has been well-documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological and clinical studies have established that high LDL-C and low high-density lipoprotein cholesterol (HDL-C) are both associated with coronary heart disease. However, the risk of developing coronary heart disease is continuous and graded over the range of cholesterol levels and many coronary events do occur in patients with total cholesterol (total-C) and LDL-C in the lower end of this range.

MEVACOR has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very low-density lipoprotein (VLDL) and is catabolized predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of MEVACOR may involve both reduction of VLDL-C concentration, and induction of the LDL receptor, leading to reduced production and*/*or increased catabolism of LDL-C. 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-C, and modestly reduces VLDL-C and plasma triglycerides (TG) (see Tables II-III-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 strong 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 ^{14}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 ^{14}C-metabolites) peaked at 2 hours and declined rapidly to about 10% of peak by 24 hours postdose. 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.

In a study including 16 elderly patients between 70-78 years of age who received MEVACOR 80 mg/day, the mean plasma level of HMG-CoA reductase inhibitory activity was increased approximately 45% compared with 18 patients between 18-30 years of age (see PRECAUTIONS, *Geriatric Use*).

Although the mechanism is not fully understood, cyclosporine has been shown to increase the AUC of HMG-CoA reductase inhibitors. The increase in AUC for lovastatin and lovastatin acid is presumably due, in part, to inhibition of CYP3A4.

The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Potent Strong inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*).

Lovastatin is a substrate for cytochrome P450 isoform 3A4 (CYP3A4) (see PRECAUTIONS, *Drug Interactions*). Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase

the plasma concentrations of drugs metabolized by CYP3A4. In one study**, 10 subjects consumed 200 mL of double-strength grapefruit juice (one can of frozen concentrate diluted with one rather than 3 cans of water) three times daily for 2 days and an additional 200 mL double-strength grapefruit juice together with and 30 and 90 minutes following a single dose of 80 mg lovastatin on the third day. This regimen of grapefruit juice resulted in a mean increase in the serum concentration of lovastatin and its β-hydroxyacid metabolite (as measured by the area under the concentration-time curve) of 15-fold and 5-fold, respectively [as measured using a chemical assay — high performance liquid chromatography]. In a second study, 15 subjects consumed one 8 oz glass of single-strength grapefruit juice (one can of frozen concentrate diluted with 3 cans of water) with breakfast for 3 consecutive days and a single dose of 40 mg lovastatin in the evening of the third day. This regimen of grapefruit juice resulted in a mean increase in the plasma concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [using an enzyme inhibition assay both before (for active inhibitors) and after (for total inhibitors) base hydrolysis] of 1.34-fold and 1.36-fold, respectively, and of lovastatin and its β-hydroxyacid metabolite [measured using a chemical assay — liquid chromatography/tandem mass spectrometry — different from that used in the first** study] of 1.94-fold and 1.57-fold, respectively. The effect of amounts of grapefruit juice between those used in these two studies on lovastatin pharmacokinetics has not been studied.

TABLE I
The Effect of Other Drugs on Lovastatin Exposure When Both Were Co-administered

	Number of Subjects	**Dosing of Coadministered Drug or Grapefruit Juice**	**Dosing of Lovastatin**	**AUC Ratio* (with / without coadministered drug) No Effect = 1.00**	
				Lovastatin	**Lovastatin acid†**
Gemfibrozil	11	600 mg BID for 3 days	40 mg	0.96	2.80
Itraconazole‡	12	200 mg QD for 4 days	40 mg on Day 4	> 36§	22
	10	100 mg QD for 4 days	40 mg on Day 4	> 14.8§	15.4
Grapefruit Juice¶ (high dose)	10	200 mL of double-strength TID#	80 mg single dose	15.3	5.0
Grapefruit Juice¶ (low dose)	16	8 oz (about 250 mL) of single-strengthÞ for 4 days	40 mg single dose	1.94	1.57
Cyclosporine	16	Not describedß	10 mg QD for 10 days	5- to 8-fold	NDà
	Number of Subjects	**Dosing of Coadministered Drug or Grapefruit Juice**	**Dosing of Lovastatin**	**AUC Ratio* (with / without coadministered drug) No Effect = 1.00**	
				Total Lovastatin acidè	
Diltiazem	10	120 mg BID for 14 days	20 mg	3.57è	

* Results based on a chemical assay.

† Lovastatin acid refers to the β-hydroxyacid of lovastatin.

‡ The mean total AUC of lovastatin without itraconazole phase could not be determined accurately. Results could be representative of strong CYP3A4 inhibitors such as ketoconazole, posaconazole, clarithromycin, telithromycin, HIV protease inhibitors, and nefazodone.

§ Estimated minimum change.

¶ The effect of amounts of grapefruit juice between those used in these two studies on lovastatin pharmacokinetics has not been studied.

Double-strength: one can of frozen concentrate diluted with one can of water. Grapefruit juice was administered TID for 2 days, and 200 mL together with single dose lovastatin and 30 and 90 minutes following single dose lovastatin on Day 3.

Þ Single-strength: one can of frozen concentrate diluted with 3 cans of water. Grapefruit juice was administered with breakfast for 3 days, and lovastatin was administered in the evening on Day 3.

ß Cyclosporine-treated patients with psoriasis or post kidney or heart transplant patients with stable graft function, transplanted at least 9 months prior to study.

à ND = Analyte not determined.

** Kantola, T, et al., Clin Pharmacol Ther 1998; 63(4):397-402.

è Lactone converted to acid by hydrolysis prior to analysis. Figure represents total unmetabolized acid and lactone.

Clinical Studies in Adults

MEVACOR has been shown to be highly effective in reducing total-C and LDL-C 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 plasma total-C, LDL-C, total-C/HDL-C ratio and LDL-C/HDL-C ratio. In addition, MEVACOR produced increases of variable magnitude in HDL-C, and modestly decreased VLDL-C and plasma TG (see Tables II through ~~III~~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 6 Weeks)

DOSAGE	N	TOTAL-C	LDL-C	HDL-C	LDL-C/ HDL-C	TOTAL-C/ HDL-C	TG.
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	–19	–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	–6

MEVACOR was compared to cholestyramine in a randomized open parallel study. The study was performed with patients with hypercholesterolemia who were at high risk of myocardial infarction. Summary results are presented in Table II.

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)	TG. (mean)
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 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-C 240-300 mg/dL [6.2 mmol/L - 7.6 mmol/L], LDL-C >160 mg/dL [4.1 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. All changes in the lipid measurements (Table ~~III~~IV) in MEVACOR treated patients were dose-related and significantly different from placebo ($p \leq 0.001$). These results were sustained throughout the study.

TABLE ~~III~~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)	TG. (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.	1645	–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

Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)

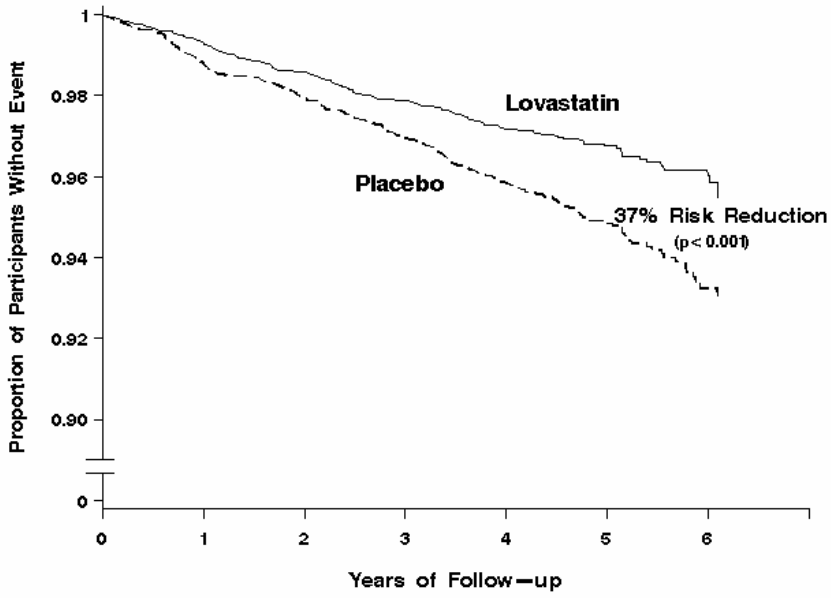
The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), a double-blind, randomized, placebo-controlled, primary prevention study, demonstrated that treatment with MEVACOR decreased the rate of acute major coronary events (composite endpoint of myocardial infarction, unstable angina, and sudden cardiac death) compared with placebo during a median of 5.1 years of follow-up. Participants were middle-aged and elderly men (ages 45-73) and women (ages 55-73) without symptomatic cardiovascular disease with average to moderately elevated total-C and LDL-C, below average HDL-C, and who were at high risk based on elevated total-C/HDL-C. In addition to age, 63% of the participants had at least one other risk factor (baseline HDL-C <35 mg/dL, hypertension, family history, smoking and diabetes).

AFCAPS/TexCAPS enrolled 6,605 participants (5,608 men, 997 women) based on the following lipid entry criteria: total-C range of 180-264 mg/dL, LDL-C range of 130-190 mg/dL, HDL-C of ≤45 mg/dL for men and ≤47 mg/dL for women, and TG of ≤400 mg/dL. Participants were treated with standard care, including diet, and either MEVACOR 20-40 mg daily (n= 3,304) or placebo (n= 3,301). Approximately 50% of the participants treated with MEVACOR were titrated to 40 mg daily when their LDL-C remained >110 mg/dL at the 20-mg starting dose.

MEVACOR reduced the risk of a first acute major coronary event, the primary efficacy endpoint, by 37% (MEVACOR 3.5%, placebo 5.5%; p<0.001; Figure 1). A first acute major coronary event was defined as myocardial infarction (54 participants on MEVACOR, 94 on placebo) or unstable angina (54 vs. 80) or sudden cardiac death (8 vs. 9). Furthermore, among the secondary endpoints, MEVACOR reduced the risk of unstable angina by 32% (1.8 vs. 2.6%; p=0.023), of myocardial infarction by 40% (1.7 vs. 2.9%; p=0.002), and of undergoing coronary revascularization procedures (e.g., coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 33% (3.2 vs. 4.8%; p=0.001). Trends in risk reduction associated with treatment with MEVACOR were consistent across men and women, smokers and non-smokers, hypertensives and non-hypertensives, and older and younger participants. Participants with ≥2 risk factors had risk reductions (RR) in both acute major coronary events (RR 43%) and coronary revascularization procedures (RR 37%). Because there were too few events among those participants with age as their only risk factor in this study, the effect of MEVACOR on outcomes could not be adequately assessed in this subgroup.

Figure 1

Acute Major Coronary Events
(Primary Endpoint)



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 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.

Clinical Studies in Adolescent Patients

Efficacy of Lovastatin in Adolescent Boys with Heterozygous Familial Hypercholesterolemia

In a double-blind, placebo-controlled study, 132 boys 10-17 years of age (mean age 12.7 yrs) with heterozygous familial hypercholesterolemia (heFH) were randomized to lovastatin (n=67) or placebo (n=65) for 48 weeks. Inclusion in the study required a baseline LDL-C level between 189 and 500 mg/dL and at least one parent with an LDL-C level >189 mg/dL. The mean baseline LDL-C value was 253.1 mg/dL (range: 171-379 mg/dL) in the MEVACOR group compared to 248.2 mg/dL (range: 158.5-413.5 mg/dL) in the placebo group. The dosage of lovastatin (once daily in the evening) was 10 mg for the first 8 weeks, 20 mg for the second 8 weeks, and 40 mg thereafter.

MEVACOR significantly decreased plasma levels of total-C, LDL-C and apolipoprotein B (see Table ~~IV~~<u>V</u>).

TABLE ~~IV~~<u>V</u>
<u>Lipid-lowering Effects of Lovastatin in Adolescent Boys with Heterozygous Familial Hypercholesterolemia</u>
(Mean Percent Change from Baseline at Week 48 in Intention-to-Treat Population)

DOSAGE	N	TOTAL-C	LDL-C	HDL-C	TG.*	Apolipoprotein B
Placebo	61	-1.1	-1.4	-2.2	-1.4	-4.4
MEVACOR	64	-19.3	-24.2	+1.1	-1.9	-21

*data presented as median percent changes

The mean achieved LDL-C value was 190.9 mg/dL (range: 108-336 mg/dL) in the MEVACOR group compared to 244.8 mg/dL (range: 135-404 mg/dL) in the placebo group.

Efficacy of Lovastatin in Post-Menarchal Girls with Heterozygous Familial Hypercholesterolemia

In a double-blind, placebo-controlled study, 54 girls 10-17 years of age who were at least 1 year post-menarche with heFH were randomized to lovastatin (n=35) or placebo (n=19) for 24 weeks. Inclusion in the study required a baseline LDL-C level of 160-400 mg/dL and a parental history of familial hypercholesterolemia. The mean baseline LDL-C value was 218.3 mg/dL (range: 136.3-363.7 mg/dL) in the MEVACOR group compared to 198.8 mg/dL (range: 151.1-283.1 mg/dL) in the placebo group. The dosage of lovastatin (once daily in the evening) was 20 mg for the first 4 weeks, and 40 mg thereafter.

MEVACOR significantly decreased plasma levels of total-C, LDL-C, and apolipoprotein B (see Table V<u>I</u>).

TABLE V<u>I</u>
<u>Lipid-lowering Effects of Lovastatin in Post-Menarchal Girls with Heterozygous Familial Hypercholesterolemia</u>
(Mean Percent Change from Baseline at Week 24 in Intention-to-Treat Population)

DOSAGE	N	TOTAL-C	LDL-C	HDL-C	TG.*	Apolipoprotein B
Placebo	18	+3.6	+2.5	+4.8	-3.0	+6.4
MEVACOR	35	-22.4	-29.2	+2.4	-22.7	-24.4

*data presented as median percent changes

The mean achieved LDL-C value was 154.5 mg/dL (range: 82-286 mg/dL) in the MEVACOR group compared to 203.5 mg/dL (range: 135-304 mg/dL) in the placebo group.

The safety and efficacy of doses above 40 mg daily have not been studied in children. The long-term efficacy of lovastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

INDICATIONS AND USAGE

Therapy with MEVACOR should be a component of multiple risk factor intervention in those individuals with dyslipidemia at risk for atherosclerotic vascular disease. MEVACOR should be used in addition to a diet restricted in saturated fat and cholesterol as part of a treatment strategy to lower total-C and LDL-C to target levels when the response to diet and other nonpharmacological measures alone has been inadequate to reduce risk.

Primary Prevention of Coronary Heart Disease

In individuals without symptomatic cardiovascular disease, average to moderately elevated total-C and LDL-C, and below average HDL-C, MEVACOR is indicated to reduce the risk of:

- Myocardial infarction
- Unstable angina
- Coronary revascularization procedures

(See CLINICAL PHARMACOLOGY, *Clinical Studies*.)

Coronary Heart Disease

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

Hypercholesterolemia

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-C and LDL-C 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.

Adolescent Patients with Heterozygous Familial Hypercholesterolemia

MEVACOR is indicated as an adjunct to diet to reduce total-C, LDL-C and apolipoprotein B levels in adolescent boys and girls who are at least one year post-menarche, 10-17 years of age, with heFH if after an adequate trial of diet therapy the following findings are present:

1. LDL-C remains >189 mg/dL or
2. LDL-C remains >160 mg/dL <u>and:</u>
    - there is a positive family history of premature cardiovascular disease or

*** Classification of Hyperlipoproteinemias

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

IDL = intermediate-density lipoprotein.

- two or more other CVD risk factors are present in the adolescent patient

General Recommendations

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 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-C – [0.2 × (TG) + 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:

NCEP Treatment Guidelines:
LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes
and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD† or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)††
2+ Risk factors (10 year risk ≤20%)	<130	≥130	10-year risk 10-20%: ≥130 10-year risk <10%: ≥ 160
0-1 Risk factor†††	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

† CHD, coronary heart disease

†† Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

††† Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dL, non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C is ≥130 mg/dL (see NCEP Guidelines above).

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-C levels in patients with combined hypercholesterolemia and hypertriglyceridemia where hypercholesterolemia is the major abnormality (Type IIb hyperlipoproteinemia), it has not been studied in conditions where the major abnormality is elevation of chylomicrons, VLDL or IDL (i.e., hyperlipoproteinemia types I, III, IV, or V).***

The NCEP classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature cardiovascular disease is summarized below:

Category	Total-C (mg/dL)	LDL-C (mg/dL)
Acceptable	<170	<110
Borderline	170-199	110-129
High	≥200	≥130

Children treated with lovastatin in adolescence should be re-evaluated in adulthood and appropriate changes made to their cholesterol-lowering regimen to achieve adult goals for LDL-C.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

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

<u>Concomitant administration with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone) (see WARNINGS, *Myopathy/Rhabdomyolysis)*.</u>

Pregnancy and lactation (see PRECAUTIONS, *Pregnancy* and *Nursing Mothers*). 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 is contraindicated during pregnancy and in nursing mothers. **MEVACOR 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, MEVACOR should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see PRECAUTIONS, *Pregnancy*).

WARNINGS

Myopathy/Rhabdomyolysis

Lovastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related. In a clinical study (EXCEL) in which patients were carefully monitored and some interacting drugs were excluded, there was one case of myopathy among 4933 patients randomized to lovastatin 20-40 mg daily for 48 weeks, and 4 among 1649 patients randomized to 80 mg daily.

All patients starting therapy with lovastatin, or whose dose of lovastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Lovastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. In most cases, muscle symptoms and CK increases resolved when treatment was promptly discontinued. Periodic CK determinations may be considered in patients starting therapy with lovastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

Many of the patients who have developed rhabdomyolysis on therapy with lovastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. ~~Therapy with lovastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.~~<u>MEVACOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. MEVACOR therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.</u>

The risk of myopathy/rhabdomyolysis is increased by concomitant use of lovastatin with the following:

~~Potent~~ <u>Strong</u> inhibitors of CYP3A4: Lovastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of cytochrome P450 3A4 (CYP3A4). ~~When lovastatin is used with a potent~~

inhibitor of CYP3A4, elevated plasma levels of HMG-CoA reductase inhibitory activity can increase the risk of myopathy and rhabdomyolysis, particularly with higher doses of lovastatin.

The use of lovastatin concomitantly with the potent CYP3A4 inhibitors itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) should be avoided. Concomitant use of other medicines labeled as having a potent inhibitory effect on CYP3A4 should be avoided unless the benefits of combined therapy outweigh the increased risk.Certain drugs which inhibit this metabolic pathway can raise the plasma levels of lovastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, and posaconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, boceprevir, telaprevir, or the antidepressant nefazodone. Combination of these drugs with lovastatin is contraindicated. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with lovastatin should be suspended during the course of treatment (see CONTRAINDICATIONS; PRECAUTIONS, *Drug Interactions*).

Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentration of lovastatin. It is recommended that dose adjustment of lovastatin be considered during coadministration. Increased lovastatin concentration in plasma has been associated with an increased risk of myopathy/rhabdomyolysis.

Gemfibrozil, particularly with higher doses of lovastatin: The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with gemfibrozil. The combined use of lovastatin with gemfibrozil should be avoided, unless the benefits are likely to outweigh the increased risks of this drug combination.

Other lipid-lowering drugs (other fibrates or ≥1 g/day of niacin): The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with other fibrates or ≥1 g/day of niacin. Caution should be used when prescribing other fibrates or lipid-lowering doses (≥1 g/day) of niacin with lovastatin, as these agents can cause myopathy when given alone. **The benefit of further alterations in lipid levels by the combined use of lovastatin with other fibrates or niacin should be carefully weighed against the potential risks of these combinations.**

Cyclosporine: The use of lovastatin with cyclosporine should be avoided.

Cyclosporine or dDanazol, diltiazem or verapamil with higher doses of lovastatin: The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with cyclosporine or danazol, diltiazem, or verapamil. The benefits of the use of lovastatin in patients receiving cyclosporine or danazol, diltiazem, or verapamil should be carefully weighed against the risks of these combinations.

Amiodarone or verapamil: The dose of lovastatin should not exceed 40 mg daily in patients receiving concomitant medication with amiodarone or verapamil. The combined use of lovastatin at doses higher than 40 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy. The risk of myopathy/rhabdomyolysis is increased when either amiodarone or verapamil is used concomitantly with higher doses of a closely related member of the HMG-CoA reductase inhibitor class.

Colchicine: Cases of myopathy, including rhabdomyolysis, have been reported with lovastatin coadministered with colchicine, and caution should be exercised when prescribing lovastatin with colchicine (see PRECAUTIONS, *Drug Interactions*).

Ranolazine: The risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of ranolazine. Dose adjustment of lovastatin may be considered during co-administration with ranolazine.

Prescribing recommendations for interacting agents are summarized in Table VII (see also CLINICAL PHARMACOLOGY, *Pharmacokinetics*; PRECAUTIONS, *Drug Interactions*; DOSAGE AND ADMINISTRATION).

Table VII
Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Strong CYP3A4 inhibitors, e.g.: Ketoconazole Itraconazole ~~Ketoconazole~~ Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Boceprevir Telaprevir Nefazodone	~~Avoid~~Contraindicated with lovastatin
Gemfibrozil Cyclosporine	Avoid with lovastatin
~~Gemfibrozil~~ ~~Other fibrates~~ ~~Lipid-lowering doses (≥1 g/day) of niacin~~ ~~Cyclosporine~~ Danazol Diltiazem Verapamil	Do not exceed 20 mg lovastatin daily
Amiodarone ~~Verapamil~~	Do not exceed 40 mg lovastatin daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

Liver Dysfunction

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 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).

In AFCAPS/TexCAPS, the number of participants with consecutive elevations of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (> 3 times the upper limit of normal), over a median of 5.1 years of follow-up, was not significantly different between the MEVACOR and placebo groups (18 [0.6%] vs. 11 [0.3%]). The starting dose of MEVACOR was 20 mg/day; 50% of the MEVACOR treated participants were titrated to 40 mg/day at Week 18. Of the 18 participants on MEVACOR with consecutive elevations of either ALT or AST, 11 (0.7%) elevations occurred in participants taking 20 mg/day, while 7 (0.4%) elevations occurred in participants titrated to 40 mg/day. Elevated transaminases resulted in discontinuation of 6 (0.2%) participants from therapy in the MEVACOR group (n=3,304) and 4 (0.1%) in the placebo group (n=3,301).

~~It is recommended that liver function tests be performed prior to initiation of therapy in patients with a history of liver disease, or when otherwise clinically indicated. It is recommended that liver function tests be performed in all patients prior to use of 40 mg or more daily and thereafter when clinically indicated. 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) returns 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.It is recommended that liver enzyme tests be obtained prior to initiating therapy with MEVACOR and repeated as clinically indicated.

There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including lovastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with MEVACOR, promptly interrupt therapy. If an alternate etiology is not found do not restart MEVACOR.

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.

PRECAUTIONS

General

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 about substances they should not take concomitantly with lovastatin and be advised to report promptly unexplained muscle pain, tenderness, or weakness (see list below and WARNINGS, *Myopathy/Rhabdomyolysis*). Patients should also be advised to inform other physicians prescribing a new medication that they are taking MEVACOR.

It is recommended that liver enzymes be checked before starting therapy, and if signs or symptoms of liver injury occur. All patients treated with MEVACOR should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.

Drug Interactions

CYP3A4 Interactions

Lovastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. PotentStrong inhibitors of CYP3A4 (below)e.g., itraconazole, ketoconazole, posaconazole, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone, and erythromycin), and large quantities of grapefruit juice (>1 quart daily) increase the risk of myopathy by reducing the elimination of lovastatin.

(See CONTRAINDICATIONS, WARNINGS, *Myopathy/Rhabdomyolysis*, and CLINICAL PHARMACOLOGY, *Pharmacokinetics*.)

Itraconazole
Ketoconazole
Erythromycin
Clarithromycin
Telithromycin
HIV protease inhibitors

~~Nefazodone~~
~~Large quantities of grapefruit juice (>1 quart daily)~~

In vitro studies have demonstrated that voriconazole inhibits the metabolism of lovastatin. Adjustment of the lovastatin dose may be needed to reduce the risk of myopathy, including rhabdomyolysis, if voriconazole must be used concomitantly with lovastatin.

Interactions With Lipid-Lowering Drugs That Can Cause Myopathy When Given Alone

The risk of myopathy is also increased by the following lipid-lowering drugs that are not ~~potent~~ strong CYP3A4 inhibitors, but which can cause myopathy when given alone.

See WARNINGS, *Myopathy/Rhabdomyolysis.*
Gemfibrozil
Other fibrates
Niacin (nicotinic acid) (≥1 g/day)

Other Drug Interactions

Cyclosporine: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine (see WARNINGS, *Myopathy/Rhabdomyolysis*).

~~*Cyclosporine or Danazol, Diltiazem, or Verapamil:*~~ The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ~~cyclosporine or~~ danazol, diltiazem, or verapamil particularly with higher doses of lovastatin (see WARNINGS, *Myopathy/Rhabdomyolysis*; CLINICAL PHARMACOLOGY, *Pharmacokinetics*).

~~*Amiodarone or Verapamil*~~: The risk of myopathy/rhabdomyolysis is increased when ~~either~~ amiodarone ~~or verapamil~~ is used concomitantly with a closely related member of the HMG-CoA reductase inhibitor class (see WARNINGS, *Myopathy/Rhabdomyolysis*).

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-second 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.

Colchicine: Cases of myopathy, including rhabdomyolysis, have been reported with lovastatin coadministered with colchicine. See WARNINGS, *Myopathy/Rhabdomyolysis.*

Ranolazine: The risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of ranolazine. See WARNINGS, *Myopathy/Rhabdomyolysis*.

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*).

Endocrine Function

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including MEVACOR.

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 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,~~ 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.

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 in offspring of pregnant mice and rats dosed during gestation at 80 mg/kg/day (affected mouse fetuses/total: 8/307 compared to 4/289 in the control group; affected rat fetuses/total: 6/324 compared to 2/308 in the control group). Female rats dosed before mating through gestation at 80 mg/kg/day also had fetuses with skeletal malformations (affected fetuses/total: 1/152 compared to 0/171 in the control group). The 80 mg/kg/day dose in mice is 7 times the human dose based on body surface area and in rats results in 5 times the human exposure based on AUC. In pregnant rats given doses of 2, 20, or 200 mg/kg/day and treated through lactation, the following effects were observed: neonatal mortality (4.1%, 3.5%, and 46%, respectively, compared to 0.6% in the control group), decreased pup body weights throughout lactation (up to 5%, 8%, and 38%, respectively, below control), supernumerary ribs in dead pups (affected fetuses/total: 0/7, 1/17, and 11/79, respectively, compared to 0/5 in the control group), delays in ossification in dead pups (affected fetuses/total: 0/7, 0/17, and 1/79, respectively, compared to 0/5 in the control group) and delays in pup development (delays in the appearance of an auditory startle response at 200 mg/kg/day and free-fall righting reflexes at 20 and 200 mg/kg/day).

Direct dosing of neonatal rats by subcutaneous injection with 10 mg/kg/day of the open hydroxyacid form of lovastatin resulted in delayed passive avoidance learning in female rats (mean of 8.3 trials to criterion, compared to 7.3 and 6.4 in untreated and vehicle-treated controls; no effects on retention 1 week later) at exposures 4 times the human systemic exposure at 80 mg/day based on AUC. No effect was seen in male rats. No evidence of malformations was observed when pregnant rabbits were given 5 mg/kg/day (doses equivalent to a human dose of 80 mg/day based on body surface area) or a maternally toxic dose of 15 mg/kg/day (3 times the human dose of 80 mg/day based on body surface area).

Rare clinical reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. However, in an analysis[†] of greater than 200 prospectively followed pregnancies exposed during the first trimester to MEVACOR or another closely related HMG-CoA reductase inhibitor, the incidence of congenital anomalies was comparable to that seen in the general population. This number of pregnancies was sufficient to exclude a 3-fold or greater increase in congenital anomalies over the background incidence.

Maternal treatment with MEVACOR may reduce the fetal levels of mevalonate, which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering drugs during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolemia. For these reasons, MEVACOR should not be used in women who are pregnant, or can become pregnant (see CONTRAINDICATIONS). 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. Treatment should be immediately discontinued as soon as pregnancy is recognized.

[†] Manson, J.M., Freyssinges, C., Ducrocq, M.B., Stephenson, W.P., Postmarketing Surveillance of Lovastatin and Simvastatin Exposure During Pregnancy. *Reproductive Toxicology*. 10(6):439-446. 1996.

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 patients 10-17 years of age with heFH have been evaluated in controlled clinical trials of 48 weeks duration in adolescent boys and controlled clinical trials of 24 weeks duration in girls who were at least 1 year post-menarche. Patients treated with lovastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses greater than 40 mg have not been studied in this population**. In these limited controlled studies, there was no detectable effect on growth or sexual maturation in the adolescent boys or on menstrual cycle length in girls. See CLINICAL PHARMACOLOGY, *Clinical Studies in Adolescent Patients*; ADVERSE REACTIONS, *Adolescent Patients*; and DOSAGE AND ADMINISTRATION, *Adolescent Patients (10-17 years of age) with Heterozygous Familial Hypercholesterolemia*. Adolescent females should be counseled on appropriate contraceptive methods while on lovastatin therapy (see CONTRAINDICATIONS and PRECAUTIONS, *Pregnancy*). **Lovastatin has not been studied in pre-pubertal patients or patients younger than 10 years of age.**

Geriatric Use

A pharmacokinetic study with lovastatin showed the mean plasma level of HMG-CoA reductase inhibitory activity to be approximately 45% higher in elderly patients between 70-78 years of age compared with patients between 18-30 years of age; however, clinical study experience in the elderly indicates that dosage adjustment based on this age-related pharmacokinetic difference is not needed. In the two large clinical studies conducted with lovastatin (EXCEL and AFCAPS/TexCAPS), 21% (3094/14850) of patients were ≥65 years of age. Lipid-lowering efficacy with lovastatin was at least as great in elderly patients compared with younger patients, and there were no overall differences in safety over the 20 to 80 mg/day dosage range (see CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS

MEVACOR is generally well tolerated; adverse reactions usually have been mild and transient.

Phase III Clinical Studies

In Phase III controlled clinical studies involving 613 patients treated with MEVACOR, the adverse experience profile was similar to that shown below for the 8,245-patient EXCEL study (see *Expanded Clinical Evaluation of Lovastatin [EXCEL] Study*).

Persistent increases of serum transaminases have been noted (see WARNINGS, *Liver Dysfunction*). About 11% of patients had elevations of CK levels of at least twice the normal value on one or more occasions. The corresponding values for the control agent cholestyramine was 9 percent. This was attributable to the noncardiac fraction of CK. Large increases in CK have sometimes been reported (see WARNINGS, *Myopathy/Rhabdomyolysis*).

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study

MEVACOR was compared to placebo in 8,245 patients with hypercholesterolemia (total-C 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 = 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) %
Body As a Whole					
Asthenia	1.4	1.7	1.4	1.5	1.2
Gastrointestinal					
Abdominal pain	1.6	2.0	2.0	2.2	2.5
Constipation	1.9	2.0	3.2	3.2	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	2.6	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.

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%.

Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)

In AFCAPS/TexCAPS (see CLINICAL PHARMACOLOGY, *Clinical Studies*) involving 6,605 participants treated with 20-40 mg/day of MEVACOR (n=3,304) or placebo (n=3,301), the safety and tolerability profile of the group treated with MEVACOR was comparable to that of the group treated with placebo during a median of 5.1 years of follow-up. The adverse experiences reported in AFCAPS/TexCAPS were similar to those reported in EXCEL (see ADVERSE REACTIONS, *Expanded Clinical Evaluation of Lovastatin (EXCEL) Study*).

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 gemfibrozil to therapy with lovastatin is not associated with greater reduction in LDL-C than that achieved with lovastatin alone. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with cyclosporine, gemfibrozil or niacin (nicotinic acid). The combined use of lovastatin ~~at doses exceeding 20 mg/day~~ with cyclosporine <u>or</u>~~,~~ gemfibrozil~~, other fibrates or lipid-lowering doses (≥1 g/day) of niacin~~ should be avoided<u>. Caution should be used when prescribing other fibrates or lipid-lowering doses (≥1 g/day) of niacin with lovastatin</u> (see WARNINGS, *Myopathy/Rhabdomyolysis*).

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, arthralgias.

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

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, dermatomyositis, 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, fatal and non-fatal hepatic failure.

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

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

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

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

Adolescent Patients (ages 10-17 years)

In a 48-week controlled study in adolescent boys with heFH (n=132) and a 24-week controlled study in girls who were at least 1 year post-menarche with heFH (n=54), the safety and tolerability profile of the groups treated with MEVACOR (10 to 40 mg daily) was generally similar to that of the groups treated with placebo (see CLINICAL PHARMACOLOGY, *Clinical Studies in Adolescent Patients* and PRECAUTIONS, *Pediatric Use*).

OVERDOSAGE

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

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.

DOSAGE 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.

Adult Patients

The usual recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range of lovastatin 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 CLINICAL PHARMACOLOGY). Patients requiring reductions in LDL-C 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 of lovastatin may be considered for patients requiring smaller reductions. Adjustments should be made at intervals of 4 weeks or more. The 10 mg dosage is

provided for information purposes only. Although lovastatin tablets 10 mg are available in the marketplace, MEVACOR is no longer marketed in the 10 mg strength.

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.

Dosage in Patients taking ~~Cyclosporine or~~ Danazol, Diltiazem, or Verapamil

In patients taking ~~cyclosporine or~~ danazol, diltiazem, or verapamil concomitantly with lovastatin ~~(see WARNINGS, *Myopathy/Rhabdomyolysis*)~~, therapy should begin with 10 mg of lovastatin and should not exceed 20 mg/day (see CLINICAL PHARMACOLOGY, *Pharmacokinetics,* WARNINGS, *Myopathy/Rhabdomyolysis*, PRECAUTIONS, *Drug Interactions, Other Drug Interactions*).

Dosage in Patients taking Amiodarone ~~or Verapamil~~

In patients taking amiodarone ~~or verapamil~~ concomitantly with MEVACOR, the dose should not exceed 40 mg/day (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*, *Other ~~drug interactions~~Drug Interactions*).

Adolescent Patients (10-17 years of age) with Heterozygous Familial Hypercholesterolemia

The recommended dosing range of lovastatin is 10-40 mg/day; the maximum recommended dose is 40 mg/day. Doses should be individualized according to the recommended goal of therapy (see NCEP Pediatric Panel Guidelines[††], CLINICAL PHARMACOLOGY, and INDICATIONS AND USAGE). Patients requiring reductions in LDL-C of 20% or more to achieve their goal should be started on 20 mg/day of MEVACOR. A starting dose of 10 mg of lovastatin may be considered for patients requiring smaller reductions. Adjustments should be made at intervals of 4 weeks or more.

Concomitant Lipid-Lowering Therapy

MEVACOR is effective alone or when used concomitantly with bile-acid sequestrants~~. If MEVACOR is used in combination with gemfibrozil, other fibrates or lipid-lowering doses (≥ 1g/day) of niacin, the dose of MEVACOR should not exceed 20 mg/day~~ (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*).

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, *Myopathy/Rhabdomyolysis*).

HOW SUPPLIED

No. 8123 — Tablets MEVACOR 20 mg are blue, octagonal tablets, coded MSD 731 on one side and plain on the other. They are supplied as follows:

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

No. 8124 — Tablets MEVACOR 40 mg are green, octagonal tablets, coded MSD 732 on one side and plain on the other. They are supplied as follows:

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

Storage

Store at 20-25°C (68-77°F). [See USP Controlled Room Temperature.] Tablets MEVACOR must be protected from light and stored in a well-closed, light-resistant container.

Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

By:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505, USA
OR
Mylan Pharmaceuticals ULC

[††] National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics*. 89(3):495-501. 1992.

MEVACOR® (Lovastatin) ~~9844661~~9844662
~~014-874-01~~

Etobicoke, Ontario, Canada M8Z 2S6

~~Issued May 2010~~Revised: 02/2012

9844662

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019643Orig1s085

MEDICAL REVIEW(s)

Clinical Review for Statin Class Labeling Changes

February 15, 2012
Amy G. Egan, M.D., M.P.H.

On August 11, 2011 the Division of Metabolism and Endocrinology Products (DMEP) issued supplement request letters to the sponsors of all HMG-CoA reductase inhibitor (statin) drugs requesting changes to the labeling so as to furnish adequate information for the safe and effective use of their statin. These labeling changes were based on FDA's comprehensive review of the statin class of drugs, including clinical trial data, Adverse Event Reporting System (AERS) reports, the published literature, and the labels of other approved drugs containing information on statin co-administration. This review will serve to summarize the safety issues and the sources and reviews of the data.

1. Liver enzyme abnormalities – TSI #57

On March 19, 2007 DMEP opened Tracked Safety Issue (TSI) #57 to evaluate hepatotoxicity associated with the statin class of drugs. This was based on articles in the published literature which suggested that FDA should re-evaluate current recommendations in statin labeling for routine periodic monitoring of liver enzyme tests.

In March 2008, DMEP issued Information Request letters to the statin sponsors requesting the following:

a. Does <<APPLICANT>> have an opinion or recommendation regarding the utility of baseline and/or periodic monitoring of serum aminotransferase activity prior to and/or during treatment with <<STATIN>>? Please address this question for subjects with normal liver function and for those with asymptomatic liver disease (e.g., NAFLD, hepatitis C).
b. Upon what clinical evidence or other consideration are these opinions or recommendations based?
c. Please provide the number of phase 2 and 3 trials conducted with <<STATIN>> for which you have access to the raw data.

The table below summarizes the sponsors' responses to the first question:

Table 10. Overview of Industry responses to FDA questions on hepatotoxicity of statins			
Sponsor	Product	Text suggests interest in withdrawal of monitoring	caveats
Andrx	Lovastatin ER	No	none
AstraZeneca	rosuvastatin	Yes	none
Bristol-Myers Squibb	pravastatin	N/A	No text to delete
Merck	lovastatin	No	None
Merck	simvastatin	No	None
Novartis	fluvastatin	No	None
Pfizer	atorvastatin	Yes	10 mg dose only

In general, most sponsors agreed that liver enzyme testing prior to initiation of statin therapy was appropriate, but acknowledged that there appeared to be limited utility to routine liver biochemistry monitoring during treatment. One sponsor commented on the recommendations of the Liver Expert Panel convened by the National Lipid Association which stated that "because there is no evidence that a relation exists between elevated serum aminotransferase levels and significant liver injury, or that routine monitoring of liver biochemistries will identify individuals likely to develop rare cases of idiosyncratic liver failure, the requirement for routine liver biochemistry monitoring in patients receiving any of the currently marketed statin therapies should be re examined." Another sponsor noted that "nearly 50% of hyperlipidemic patients have coexisting non-alcoholic fatty liver disease (NAFLD) and it is well known that LFT levels fluctuate in NAFLD."

In conjunction with the request to statin sponsors, DMEP requested that the Office of Surveillance and Epidemiology (OSE) conduct a review to characterize the risk of clinically serious hepatotoxicity in association with statins and assist in a determination if the statin class labeling for liver enzyme monitoring should be retained, revised, or removed. OSE had conducted 5 postmarket reviews of statins and hepatotoxicity between 2000 and 2009. Those reviews had consistently noted that reporting of statin-associated serious liver injury to AERS was extremely low (reporting rate of ≤2 per one million patient-years).

The OSE review of AERS was completed May 13, 2011. The review focused on cases of severe liver injury, defined as a 4 (severe liver injury) or a 5 (death or liver transplant) using the Drug Induced Liver Injury Network (DILIN) liver injury severity scale. Cases meeting those criteria were further assessed for causality. Seventy-five cases (27 with a severity score of 4 and 48 with a severity score of 5 [37 deaths and 11 liver transplants]) were assessed for causality, 30 of which (14 deaths, 7 liver transplantations, and 9 severe liver injury) were assessed as possibly (25-49% likelihood) or probably (50-74% likelihood) associated with

statin therapy. No cases were assessed as highly likely (75-95% likelihood) or definitely (>95% likelihood) associated with statin therapy. OSE noted that "despite rising use of statins as a class since the late 1990s, there has not been a detectable uptick in the annual rates of fatal (deaths or liver transplant) or severe liver injury possibly or probably causally associated cases." The cases are summarized in the table below:

Table 6. Characteristics of U.S. AERS Cases With A Liver Injury Severity Score of 4 (Severe) or 5 (Death or Transplant) and Causally Associated* With Statin Therapy. Source: AERS, marketing through January 1, 2009)

Liver Injury Severity Score	**5 (Death)**	**5 (Transplant)**	**4 (Severe)**
# of Cases	14	7	9
Median Age in Years (range)	66 (51-89)	48 (40-71)	58 (47-71)
Percent Female	79% (11/14)	71% (5/7)	67% (6/9)
Statin at the Time of Event Median Daily Dose in mg (range [n])			
Atorvastatin	4 -- (10, 10 [n=2])	3 10 (10-20 [n=3])	4 10 (10-20 [n=3])
Cerivastatin	--	--	--
Fluvastatin	--	--	1 – (20 [n=1])
Lovastatin	1 -- (20 [n=1])	1 -- (-- [n=0])	--
Pravastatin	3 -- (20, 40 [n=2])	--	1 – (10 [n=1])
Rosuvastatin	--	--	--
Simvastatin	6 20 (10-40 [n=5])	3 20 (20-40 [n=3])	3 – (40 [n=1])
Time to Onset in Months,** Median (range)	2.5 (3 wk – 12 mo)	1.5 (2.4 wk - 6 mo)	2 (5 wk – 8 mo)
Peak Serum Total Bilirubin Level in mg/dL, Median (range [n])	23 (2.9-51 [n=12])	27 (22-32 [n=4])	10 (1.2-25 [n=9])
Peak Serum ALT Level in units/L, Median (range[n]) reference range: 6-41 units/L	1,127 (148-4,300 [n=10])	2,912 (2,037-13,531[n=4])	1,319 (538-3,000 [n=9])
Peak Serum AST Level in units/L, Median (range[n]) reference range: 9-34 units/L	1,497 (81-7,200 [n=11])	2,294 (1,755-6,815 [n=4])	1,260 (853-3,000 [n=9])
Peak Serum ALP Level in units/L, Median (range[n]) reference range: 37-116 units/L	206 (155-623 [n=9])	-- (290, 602 [n=2])	307 (131-800 [n=4])

*Defined as probably associated (supported by the evidence as implicating the drug but not definite or highly likely) or possibly associated (causality is not supported by the preponderance of evidence, but one cannot definitively exclude the possibility)

**Time to onset defined as the interval between exposure time or time after dose increased to reported liver injury event

OSE also looked at cases from the DILIN and Acute Liver Failure Study Group (ALFSG), organizations which have been systematically submitting reports to FDA of drug associated liver injury referred to their respective liver injury outcome studies. For statin associated liver injury, DILIN has submitted 25 reports to FDA as of January 1, 2011, twelve of which resulted in an outcome of hospitalization. In the ALFSG database, there were 9 reports of drug-induced liver injury (DILI) associated with statin therapy. OSE cited a 2010 article from

ALFSG that included 133 prospectively identified cases of idiopathic DILI resulting in acute liver failure. Fifteen patients were taking statins and in 6 of these 15 individuals a statin was identified as the only potential DILI agent. The authors noted that statin hepatotoxicity is "generally benign" and the identification of these 6 cases represents a "provocative observation".

Using the AERS and drug utilization databases, reporting rates were calculated for U.S. statin cases associated with liver injury and an outcome of death or liver transplant, from the time of initial marketing approval through January 1, 2009. It should be noted that reporting rates are subject to secular reporting trends which normally preclude generation of reporting rates between products with initial marketing dates greater than 2-4 years apart. Despite the limitations of the analysis, it appears that reporting levels for serious liver injury in association with currently marketed statins are generally similar.

Table 9. Number of U.S. Statin Cases Associated with Liver Injury and an Outcome of Death or Liver Transplant (Severity Score 5). Initial Marketing Approval Through January 1, 2009

Generic Name (Brand)	Number of cases	Total Number of Prescriptions (TRxs) Dispensed by U.S. Retail Pharmacies, 1991-2008‡ (in millions)	Observed reporting rate as cases per (b) (4)
Lovastatin (Mevacor, Advicor, Altocor)	23		(b) (4)
Pravastatin (Pravachol)	11		
Simvastatin (Zocor, Vytorin, Simcor)	51		
Fluvastatin (Lescol)	4		
Atorvastatin (Lipitor)	64		
Rosuvastatin (Crestor)	3		
Total	**156**		

OSE also reviewed current monitoring guidelines including the National Lipid Association's Liver Expert Panel, which state:

> *The Liver Expert Panel does not believe that the available scientific evidence supports the routine monitoring of liver biochemistries in asymptomatic patients receiving statins. The Panel makes this recommendation because (1) irreversible liver damage resulting from statins is exceptionally rare and is likely idiosyncratic in nature, and (2) no data exist to show that routine monitoring of liver biochemistries is effective in identifying the very rare individual who may develop significant liver injury from ongoing statin therapy. In the view of the Panel, routine monitoring will instead identify patients with isolated*

increased aminotransferase levels, which could motivate physicians to alter or discontinue statin therapy, thereby placing patients at increased risk for cardiovascular events.

OSE further noted that the NLA's Statin Safety Task Force had a slightly divergent opinion and made the following recommendation:

Until there is a change in the FDA-approved prescribing information for statins, it is appropriate to continue to measure transaminase levels before starting therapy, 12 weeks after initiating therapy, after a dose increase, and periodically thereafter. However, routine monitoring of liver function tests is not supported by the available evidence and the current recommendation for monitoring needs to be reconsidered by the FDA.

The OSE review concluded:

Serious, hepatocellular DILI can be caused by statins. Although the routine monitoring of serum ALT and other markers for liver injury is vital for drug development, it does not appear to be useful in a post marketing, non study, ambulatory setting to routinely detect and prevent serious liver injury in association with statins. In place of current recommendations for serum enzyme monitoring, labeling for statins should focus on an alert to identify serious liver injury and clinical symptoms of liver injury, interruption of therapy, physician interactions, and emphasize the importance of appropriate diagnostic work up.

OSE further recommended:

It is justified that the recommendation to perform routine periodic serum ALT monitoring in all treated patients at prespecified intervals currently in place for some marketed statins be removed.

Based on these recommendations, DMEP requested the following changes to statin labeling:

Under HIGHLIGHTS OF PRESCRIBING INFORMATION, under **WARNINGS AND PRECAUTIONS**:

Liver enzyme abnormalities: Persistent elevations in hepatic transaminases can occur. Check liver enzyme tests before initiating therapy and as clinically indicated thereafter.

Under **5 WARNINGS AND PRECAUTIONS,** (b) (4)

It is recommended that liver enzyme tests be performed before the initiation of <<STATIN>> (b) (4) (b) (4)

There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including <<STATIN>>. If serious liver injury with clinical symptoms and/or

hyperbilirubinemia or jaundice occurs during treatment with <<STATIN>>, promptly interrupt therapy. If an alternate etiology is not found do not restart <<STATIN>>.

Under **6 ADVERSE REACTIONS, Post-Marketing Experience:**

(b) (4)

Under **17 PATIENT COUNSELING INFORMATION, Liver Enzymes:**

It is recommended that liver enzyme tests be (b) (4) before the initiation of <<STATIN>> and if signs or symptoms of liver injury occur. All patients treated with <<STATIN>> should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.

(b) (4)

2. Cognitive effects – TSI #772

On September 2, 2009 DMEP opened TSI #772 to evaluate the effect of statins on cognition. This was based on a complaint received from Joe Graedon of the People's Pharmacy, and an unpublished study by Duane Graveline, M.D., M.P.H. and Jay S. Cohen, M.D. entitled "Lipitor-associated memory loss: analysis of 662 cases of cognitive damage", as well as other articles from the published literature.

In attempting to assess this risk, DMEP looked initially at pre-clinical data. Several of the statin drug sponsors had performed pre-clinical cognition studies; however, those studies only address the issue of dementia syndromes, and are less helpful in addressing the issue of acute confusional states or memory impairment. Therefore, it was determined that there was no value added to re-assessing the pre-clinical data.

DMEP sent information request letters to those statin sponsors who had conducted clinical trials in which some form of neurocognitive assessment had been conducted as part of the study protocol. Those trials included: Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), Heart Protection Study (HPS), and Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH).

The findings were as follows:

- **PROSPER:** Subjects were screened with a Mini Mental Status Exam (MMSE) and excluded if their score was <24. Cognitive function was assessed in all 5,804 participants at six different time points during the study.

Four neuropsychological tests were performed, two of which tested executive function (attention and speed) and two of which tested memory (immediate and delayed). All tests showed a significant decline over time (3-year follow-up); however, there was no difference between treatment groups, pravastatin 40 mg versus placebo.

- **HPS:** A modified Telephone Interview for Cognitive Status (TICS-m) questionnaire was administered to participants during their final follow-up, either face-to-face in the clinic or over the telephone. Data were available on 8086/10269 (79%) of simvastatin-allocated subjects and 7834/10267 (76%) of placebo-allocated subjects. No significant differences were observed between the treatment groups in the percentages of participants classified as cognitively impaired (defined as a TICS-m score below 22 out of 39), either overall (23.7% simvastatin 40 mg-allocated vs. 24.2% placebo-allocated) or in subgroups defined with respect to their age at study entry (<65 years: 17.1% vs. 17.8%; 65-69 years: 25.8% vs. 25.4%; 70-80 years: 34.6% vs. 36.2%) or their previous history of cerebrovascular disease (no prior stroke: 22.8% vs. 23.3%; prior stroke: 31.9% vs. 33.3%). Nor was there any significant difference between the groups in mean TICS-m score (24.08 vs. 24.06). Similar numbers of participants in each treatment group were reported to have developed dementia during follow-up (31 [0.3%] vs. 31 [0.3%]).

  There was a slightly higher frequency of cases of Alzheimer's disease or Alzheimer's type dementia in patients on simvastatin (n=6) compared to placebo (n=3). When looking at all patients with potential diagnoses of dementia including Alzheimer's disease, confusion, disorientation, dementia or cognitive impairment, there was no difference in the frequency of patients in the simvastatin group (n=35; 0.34%) compared to placebo (n=33; 0.32%).
- **SEARCH:** Assessment of cognitive function, using the TICS-m score, was a tertiary endpoint for the folate arm of the trial. It was performed in 8891 subjects – 4473 on simvastatin 80 mg and 4418 on simvastatin 20 mg – at the final visit. There was no difference in mean TICS-m score between treatment groups (24.3 ± 4.1 for simvastatin 80 mg vs. 24.3 ± 4.3 for simvastatin 20 mg), and no difference in percentages of patients with scores <20, ≥20, <22, ≥22, <25, ≥25, <30, ≥30 between treatment groups. The TICS-m score reflects memorizing ability in large part. Verbal fluency scores also did not differ among patients allocated to simvastatin 80 mg and simvastatin 20 mg. Hearing thresholds were assessed at final follow-up and did not differ between the simvastatin groups.

  The incidence of memory loss attributed to study treatment was 17 (0.3%) in patients allocated to simvastatin 80 mg, and 8 (0.1%) in patients allocated to simvastatin 20 mg.

It should also be noted that while no formal neurocognitive assessment was performed in the Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), there was noted a

statistically significant increase in the reported adverse event of confusional state in subjects allocated to rosuvastatin 20 mg (n=8 [0.2%]) versus subjects allocated to placebo (n=4 [0.04%]).

DMEP was aware of a Phase III efficacy study of atorvastatin that had been conducted in patients with mild to moderate Alzheimer's Disease. The clinical study report for this study (Study A2581078) was requested from the sponsor and consulted to the Division of Neurology Products (DNP) for review. DNP's findings were as follows:

> *The results of Study A2581078, an adequately-designed Phase III efficacy and safety study of atorvastatin (Lipitor) in patients with mild to moderate Probable Alzheimer's Disease, provide no evidence that the administration of Lipitor results in cognitive worsening in this population; neither was there any evidence of a worsening of global function in those treated with atorvastatin in this study.*

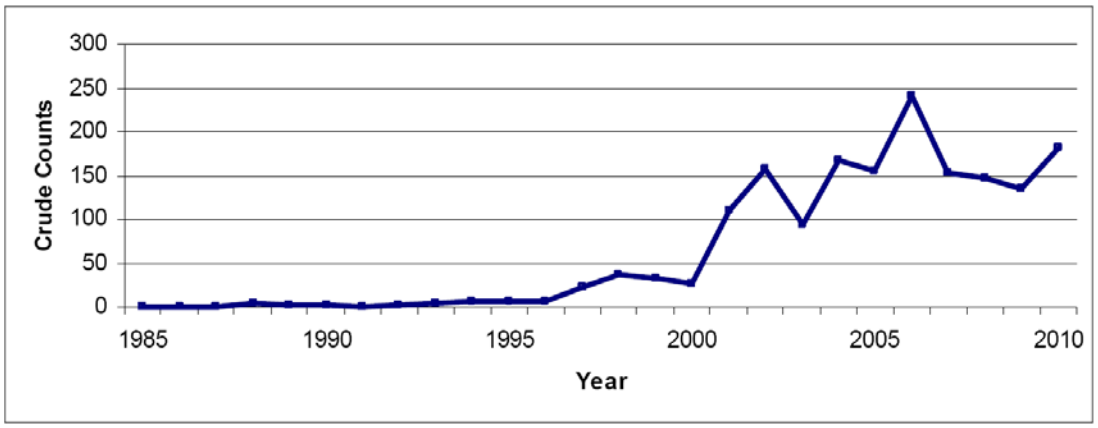
DMEP consulted OSE and requested that a review of AERS and the published literature be conducted to further assess the effect of statins on cognition. In 2002, OSE had performed a review of 279 statin reports associated with transient memory loss. This review had been requested by DMEP in response to a consumer report of transient global amnesia (TGA) with atorvastatin. At that time, OSE determined that the calculated reporting rate for statin-associated TGA (0.12-0.55 per 100,000 patient years) was well below the background incidence rate (3.4-32/100,000 population per year). As memory loss was already included in the statin labels, no labeling change was recommended at that time.

OSE's updated review of AERS focused on reports of serious cases of memory impairment, using the following High Level Terms (HLT):

- Mental Impairment (excluding dementia and memory loss)
- Memory Loss (excluding dementia)
- Amnestic Symptoms
- Confusion and Disorientation

Through January 1, 2011 there were 1,698 U.S. serious reports (crude counts) in AERS.

Figure 1. Number of U.S. Serious Statin* Reports (Crude Counts) Associated with Cognitive Change†, by Year Received. Source: AERS, Initial Marketing Approval Through January 1, 2011 (n=1,698)



*Includes single ingredient and combination statin products approved by FDA.
†Reports identified in AERS using four HLTs: Mental Impairment (excluding dementia & memory loss), Memory Loss (excluding dementia), Amnestic Symptoms, and Confusion and Disorientation

Further case review was limited to 182 reports received by FDA in 2010. Of those reports, 57 unique cases described transient cognitive change as the primary adverse event. Sixty nine percent (n=125) of the cases were excluded because they reported multiple events such as rhabdomyolysis, renal failure, and confusion (n=81), were duplicates (n=18), hearsay (n=3), reported by attorneys (n=5), or solicited reports (n=16).

Characteristics of the 57 cases included:

- Age: median of 62 years (30-85)
- Sex: 62% male
- Exposure time: median of 3 years (1 month-12 years)

The literature review included case series of transient cognitive impairment associated with statin use, as well as observational studies on the association between statin use and the incidence of dementia. The observational evidence was summarized based on a meta-analysis by Zhou and colleagues:

> *After conducting a systematic review, the authors identified four cohort studies and three case control studies which examined the association between statin use and dementia. The average observation period ranged from three to nine years. Three case control studies suggested statin use may lower the incidence of dementia; while the remaining four cohort studies failed to demonstrate an association between statin use and incident dementia. A pooled analysis also failed to demonstrate an association between statin use and incident dementia.*

OSE further noted:

Results from three prospective cohort studies published within the last year provide similar conflicting results. Analyses of Baltimore Longitudinal Study of Aging and the Ginkgo Evaluation of Memory Study suggested that statin use is associated with a lower risk of dementia. A nested case control study in the Neurological Disorders in Central Spain cohort failed to detect an association between statin use and cross sectional performance on a neuropsychological test battery.

Table 5. Observational Studies Summary: Statin Use and Cognition

Author (Publication Date)	Study Design	Total Sample Size (% Exposed to Statins)	Outcome	Key Result
Zhou (2007)	Meta-Analysis – Observational Studies	10523 (12%)	Incident Dementia	Adjusted OR=0.77 (95%: 0.45-1.30)
Beydoun (2010)	Cohort Study	1604 (7%)	Incident Dementia	Adjusted HR=0.21 (95%: 0.09-0.48)
Betterman (2011)	Cohort Study	3069 (25%)	Incident Dementia	Adjusted HR=0.79 (95%: 0.65-0.96)
Benito-Leon (2010)	Nested Case-Control	548 (25%)	Neuropsychological Test Performance	No treatment effect observed in any test neuropsychological test administered (global cognition, verbal fluency, psychomotor speed, confrontational naming, verbal memory, logical memory)

OSE concluded:

The postmarket statin reports associated with transient cognitive change generally describe individuals over the age of 50 years who experience notable (sometimes described as "dramatic"), but ill defined memory loss or impairment (e.g., "lost my mind") that is reversible upon discontinuation of statin therapy. The statin exposure time to onset of the event is highly variable (1 day to years). These cases do not appear to be associated with fixed or progressive dementia, such as Alzheimer's disease.

Like the previous (2002) OSE review, the analyzed data in this review did not reveal any discernible dose event or age (the reported age at the time of event is similar to the age of the population using statins) trends or effects between statins and other drugs; few reports described neurologic follow-up or standardized testing results. Findings from this review (and the 2002 OSE review) are also similar to patient survey results recently published by the University of California San Diego (UCSD) Statin Effects Study investigators. Cognitive issues were reported for all statins, with atorvastatin and simvastatin most frequently reported. The time to onset was variable (1 day to 10 years). Ninety percent reported symptom improvement after the statin was discontinued. Complete recovery time varied from 1 day to several years (median time to first noted improvement was 2.5 weeks). Of 29 participants who underwent rechallenge, 19 reported recurrence of events.

An analysis of the epidemiologic evidence and clinical trials did not provide evidence that chronic statin use is associated with cognitive decline at the population level. Two studies demonstrated that exposure to statins for up to six months may prevent the acquisition of a practice effect on select neuropsychological measures. However, the clinical significance of an absent practice effect in the context of normal cognitive performance is questionable. Furthermore, no study systematically assessed patients who experienced statin associated cognitive impairment during both dechallenge and rechallenge. Such systematic studies would provide additional evidence to support a causal association and better characterize the clinical phenotype.

OSE recommended that DMEP consider statin class labeling that would characterize the nature of the cognitive changes. In response, DMEP requested that the following be added to the **Adverse Reactions, Postmarketing Experience** sub-section of all statin labels:

> There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

(b) (4)

[redacted]

3. Drug-drug interaction with protease inhibitors – TSI #756

On July 23, 2009 TSI #756 was opened to examine the drug-drug interaction between statins and protease inhibitors.

In July 2009, the sponsor for rosuvastatin (CRESTOR) submitted a prior approval supplement (PAS) proposing to include information on increased rosuvastatin exposure when CRESTOR was co-administered with the combinations of protease inhibitors tipranavir/ritonavir, atazanavir/ritonavir or fosamprenavir/ritonavir, based on studies in the published literature. Previous CRESTOR labeling had noted a DDI with lopinavir/ritonavir (KALETRA) resulting in a dose cap of 10 mg of CRESTOR when co-administered with KALETRA.

In a January 2010 review of the PAS, it was noted that there were inconsistencies between the statin labels and the protease inhibitor labels regarding recommendations for co-administration of these products. It was therefore determined that the Office of Clinical Pharmacology (OCP) would review the relevant data on DDIs between statins and HIV and HCV protease inhibitors.

On August 3, 2011 OCP completed its review of the cross labeling initiative for drug interaction updates between protease inhibitors and statins. DMEP was requested to make changes to the atorvastatin and pravastatin labels to provide the results of DDI studies conducted with certain protease inhibitors, and in the case of atorvastatin, to provide dose caps where appropriate, based on the results of the following DDI studies:

- Tipranavir/ritonavir increases atorvastatin AUC and C_{max} 9.4-fold and 8.6-fold, respectively. Because clinical data demonstrating an increased risk of myopathy or rhabdomyolysis with co-administration are lacking, a contraindication was not supported and "Avoid atorvastatin" was recommended for labeling.
- Telaprevir increases atorvastatin AUC and C_{max} 7.88-fold and 10.6-fold, respectively. Because clinical data demonstrating an increased risk of myopathy or rhabdomyolysis with co-administration are lacking, a contraindication was not supported and "Avoid atorvastatin" was recommended for labeling.
- Darunavir/ritonavir increases atorvastatin AUC and C_{max} 3.4-fold and 2.25-fold, respectively. A dose cap of atorvastatin 20 mg was recommended for labeling.
- Fosamprenavir increases atorvastatin AUC and C_{max} 2.3-fold and 4.04-fold, respectively. A dose cap of atorvastatin 20 mg was recommended for labeling.

(b) (4)

(b) (4)

Based on OCP's recommendation, DMEP requested the following changes to the atorvastatin and pravastatin labels:

Atorvastatin:

Under HIGHLIGHTS OF PRESCRIBING INFORMATION, **DRUG INTERACTIONS,** Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.6, 5.1, 7, 12.3)

Interacting Agents	Prescribing Recommendations
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	~~Do not exceed 10 mg atorvastatin daily~~ Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (~~ritonavir plus~~ saquinavir plus ritonavir, ~~lopinavir plus ritonavir~~ darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir))	~~Caution when exceeding doses >20mg atorvastatin daily. The lowest dose necessary should be used.~~ Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir)	Do not exceed 40 mg atorvastatin daily

Under **DOSAGE AND ADMINISTRATION**:

2.6 Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors ~~a Combination of Ritonavir plus Saquinavir or Lopinavir plus Ritonavir~~

In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the Hepatitis C protease inhibitor (telaprevir), therapy ~~should be limited to~~ with LIPITOR ~~10 mg once daily~~ should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing LIPITOR and the lowest dose necessary employed. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of ~~ritonavir plus~~ saquinavir plus ritonavir, ~~or lopinavir plus ritonavir~~ darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir ~~for doses of~~ therapy with LIPITOR should be limited to ~~exceeding~~ 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of LIPITOR is employed. In patients with HIV taking nelfinavir, therapy with LIPITOR should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of LIPITOR is employed.

Under **5 WARNINGS AND PRECAUTIONS, 5.1 Skeletal Muscle:**

The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, the hepatitis C protease inhibitor telaprevir, combinations of HIV protease inhibitors, including ~~ritonavir plus~~ saquinavir plus ritonavir, ~~or~~ lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with LIPITOR and fibric acid derivatives, erythromycin, clarithromycin, a combination of ~~ritonavir plus~~ saquinavir plus ritonavir, ~~or~~ lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, ~~immunosuppressive drugs~~, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or 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.

Under **Table 1. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis**:

Table 1. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	~~Do not exceed 10 mg atorvastatin daily~~ Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (~~ritonavir plus~~ saquinavir plus ritonavir*, or ~~lopinavir plus ritonavir~~ darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	~~Caution when exceeding doses > 20mg atorvastatin daily. The lowest dose necessary should be used.~~ Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir)	Do not exceed 40 mg atorvastatin daily

*Use with caution and with the lowest dose necessary

Under **DRUG INTERACTIONS, Combination of Protease Inhibitors, 7.1 Strong Inhibitors of CYP 3A4:**

Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of LIPITOR ~~40 mg~~ with several combinations of HIV protease inhibitors, as well as with the Hepatitis C protease inhibitor telaprevir, ~~ritonavir plus saquinavir (400 mg twice daily) or LIPITOR 20 mg with lopinavir plus ritonavir (400 mg + 100 mg twice daily)~~ compared to that of LIPITOR alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking the HIV protease inhibitor~~s~~ tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of LIPITOR should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing LIPITOR and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the

dose of LIPITOR should not exceed 20 mg and should be used with caution. ~~caution should be used when the LIPITOR dose exceeds 20 mg~~.

Under **12 CLINICAL PHARMACOLOGY, 12.3 Pharmacokinetics, TABLE 3. Effect of Coadministered Drugs on the Pharmacokinetics of Atorvastatin:**

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC	Change in Cmax
Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	10 mg, SD	↑9.4 fold	↑8.6 fold
Nelfinavir 1250 mg BID, 14 days	10 mg QD for 28 days	↑74%	↑2.2-fold
Fosamprenavir 1400 mg BID, 14 days	10 mg QD for 4 days	↑2.3-fold	↑4.04-fold
Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	10 mg QD for 4 days	↑2.53-fold	↑2.84-fold
Darunavir 300 mg BID/ritonavir 100 mg BID, 9 days	10 mg QD for 4 days	↑3.4-fold	↑2.25-fold
Telaprevir 750 mg q8h, 10 days	20 mg, SD	↑7.88-fold	↑10.6-fold

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC	Change in Cmax
#, ‡ Ritonavir Saquinavir 400 mg BID/saquinavir ritonavir 400 mg BID, 15 days	40 mg QD for 4 days	↑3.9-fold	↑4.3-fold

‡The dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore caution should be applied and the lowest dose necessary should be used.

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC[&]	Change in Cmax[&]
~~#Lopinavir 400 mg BID/ ritonavir 100 mg BID, 14 days~~	~~20 mg QD for 4 days~~	~~↑ 5.9 fold~~	~~↑ 4.7 fold~~

Under **12 CLINICAL PHARMACOLOGY, 12.3 Pharmacokinetics, TABLE 4. Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs:**

Atorvastatin	Co-administered drug and dosing regimen		
	Drug/Dose (mg)	Change in AUC	Change in Cmax
10 mg, SD	Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	No change	No change
10 mg QD for 4 days	Fosamprenavir 1400 mg BID, 14 days	↓27%	↓18%
10 mg QD for 4 days	Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	No change	No change

Pravastatin:

Under **12 CLINICAL PHARMACOLOGY, 12.2 Pharmacokinetics, Table 3: Effect of Coadministered Drugs on the Pharmacokinetics of Pravastatin:**

Coadministered Drug and Dosing Regimen	Pravastatin		
	Dose (mg)	Change in AUC	Change in C_{max}
Darunavir 600 mg BID/Ritonavir 100 mg BID for 7 days	40 mg single dose	↑81%	↑63%
Kaletra 400 mg/100 mg BID for 14 days	20 mg OD for 4 days	↑33%	↑26%

Under **12 CLINICAL PHARMACOLOGY, 12.2 Pharmacokinetics, Table 4: Effect of Pravastatin on the Pharmacokinetics of Coadministered Drugs**

Pravastatin Dosing Regimen	Name and Dose	Change in AUC	Change in C_{max}
20 mg OD for 4 days	Kaletra 400 mg/100 mg BID for 14 days	No change	No change

A December 6, 2011 OCP review of DDI's with lovastatin noted that available data support a contraindication with strong CYP3A4 inhibitors, such as the HIV protease inhibitors. The data were summarized as follows:

- *According to the Guidance for Industry Drug Interaction Studies, lovastatin is listed as one of the sensitive in vivo CYP3A4 substrates. Therefore, strong CYP3A4 inhibitors are predicted to significantly increase lovastatin exposure because lovastatin is extensively metabolized by CYP3A4 isozyme.*
- *Literature survey indicates that itraconazole increases lovastatin exposure up to 15- to 20-fold and the drug interaction seems to result in rhabdomyolysis. Itraconazole is the representative strong CYP3A4 inhibitor and therefore, the effect of itraconazole on lovastatin exposure can be extrapolated to other strong CYP3A4 inhibitors listed in the Guidance as well as the FDA website.*

- *Strong CYP3A4 inhibitors are contraindicated for simvastatin because of the significant drug interaction and its potential for the increased risk on the rhabdomyolysis. Physicochemical and pharmacokinetic properties of lovastatin are comparable with those of simvastatin. Meanwhile, itraconazole increased the exposure of lovastatin (up to 20-fold) more than that of simvastatin (up to 13-fold), and it indicates that strong CYP3A4 inhibitor can cause greater lovastatin exposure increase compared to that of simvastatin. Therefore, it seems reasonable to extrapolate the effect of strong CYP3A4 inhibitors on simvastatin to that on lovastatin.*

Therefore, concomitant use of lovastatin with HIV protease inhibitors, as well as the HCV protease inhibitors boceprevir and telaprevir, will be contraindicated.

Lovastatin:

Under **CONTRAINDICATIONS:**

Concomitant administration with strong CYP3A4 inhibitors, e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone)

Under **WARNINGS,** ***Myopathy/Rhabdomyolysis,*** **Strong inhibitors of CYP3A4:**

Lovastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of cytochrome P450 3A4 (CYP3A4). ~~When lovastatin is used with a strong inhibitor of CYP3A4, elevated plasma levels of HMG-CoA reductase inhibitory activity can increase the risk of myopathy and rhabdomyolysis, particularly with higher doses of lovastatin.~~ Certain drugs which inhibit this metabolic pathway can raise the plasma levels of lovastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, and posaconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, boceprevir, telaprevir, or the antidepressant nefazodone. Combination of these drugs with lovastatin is contraindicated.

Under **WARNINGS,** ***Myopathy/Rhabdomyolysis,*** Table VII: Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis**:**

Interacting Agents	**Prescribing Recommendations**
Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Boceprevir Telaprevir Nefazodone	~~Avoid~~ Contraindicated with lovastatin

Under **PRECAUTIONS**, *Drug Interactions, CYP3A4 Interactions*:

Lovastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Strong inhibitors of CYP3A4 (e.g., ~~below~~ itraconazole, ketoconazole, posaconazole, clarithromycin, telithromycin, HIV protease inhibitors, bocprevir, telaprevir, nefazodone), and erythromycin, and large quantities of grapefruit juice increase the risk of myopathy by reducing the elimination of lovastatin.

~~**Itraconazole**~~
~~**Ketoconazole**~~
~~**Erythromycin**~~
~~**Clarithromycin**~~
~~**Telithromycin**~~
~~**HIV protease inhibitors**~~
~~**Nefazodone**~~
~~**Large quantities of grapefruit juice (>1 quart daily)**~~

4. Increases in HbA1c and fasting plasma glucose – TSI #891

On April 8, 2010 TSI #891 was opened to evaluate the effect of statins on increases in HbA1c and fasting plasma glucose. This was based on findings from the JUPITER trial, which reported a 27% increase in investigator-reported diabetes mellitus in rosuvastatin-exposed subjects compared to placebo-exposed subjects. High-dose atorvastatin had previously been associated with worsening glycemic control in the PROVE-IT TIMI 22 substudy.

Several articles from the published literature were also considered, including:

- Sattar N et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomized statin trials. *Lancet.*2010;375:735-742
- Sukhija R et al. Effect of Statins on Fasting Plasma Glucose in Diabetic and Nondiabetic Patients. *Journal of Investigative Medicine.*2009;57(3): 495-499
- Rajpathak SN et al. Statin Therapy and Risk of Developing Type 2 Diabetes: A Meta-Analysis. *Diabetes Care.*2009;32:1924-1929
- Koh KK et al. Atorvastatin Causes Insulin Resistance and Increases Ambient Glycemia in Hypercholesterolemic Patients. *JACC.*2010;55(12):1209-1216
- Thongtang N et al. Effects of Maximal Atorvastatin and Rosuvastatin Treatment on Markers of Glucose Homeostasis and Inflammation. *Am J Cardiol.*2011;107:387-392
- Kostapanos MS et al. Do Statins Beneficially or Adversely Affect Glucose Homeostasis? *Current Vascular Pharmacology.*2010;8:612-631
- Mills EJ et al. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170255 patients from 76 randomized trials. *Q J Med.*2011;104:109-124

- Culver AL et al. Statin Use and Risk of Diabetes Mellitus in Postmenopausal Women in the Women's Health Initiative. *Arch Intern Med*. Published online January 9, 2012.

The Sattar meta-analysis, which looked at 13 statin trials with 91,140 participants, reported that "statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio [OR] 1.09; 95% CI 1.02-1.17), with little heterogeneity (I^2=11%) between trials."

The Rajpathak meta-analysis, which looked at 6 statin trials with 57,593 participants, reported a "small increase in diabetes risk" (relative risk [RR] 1.13; 95% CI 1.03-1.23), with "no evidence of heterogeneity across trials".

The Mills meta-analysis, which looked at 76 randomized clinical trials (RCTs) with 170,255 participants, reported that 17 RCTs reported on increased risk of development of incident diabetes (Odds ratio [OR] 1.09; 95% CI 1.02-1.17, p=0.001, I^2=11%).

Culver et al looked at postmenopausal women participating in the Women's Health Initiative (WHI) to investigate whether the incidence of new-onset diabetes mellitus is associated with statin use. The study involved 153,840 women. Statin use at baseline was associated with an increased risk of DM (hazard ratio [HR], 1.71; 95% CI, 1.61-1.83); the multivariate-adjusted HR was 1.48; 95% CI, 1.38-1.59. The association was observed for all types of statin medications.

At the time of approval of the JUPITER supplement, the following labeling was required for CRESTOR:

> **5.5 Endocrine Effects**
> Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including CRESTOR.

The data for an effect of statins on incident diabetes, and increases in HbA1c and/or fasting plasma glucose seem to indicate a class effect; however, given the limitations of epidemiological data, and the findings from the West of Scotland Coronary Prevention Study (WOSCOPS) clinical trial, which suggested that pravastatin may decrease the incidence of diabetes by 30%, the division did not seek a labeling change for pravastatin.

Therefore, based on clinical trial data, epidemiological data, and the published literature, the following labeling change was requested for all statins except pravastatin:

> **5.X Endocrine Function:**
> Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including <<STATIN>>.

5. Drug-drug interaction with ranolazine – TSI #988

TSI #988 was opened by the Division of Cardiovascular and Renal Products (DCRP) in July 2010 when during routine data monitoring of the AERS database for cases of ranolazine and torsades de pointes, a signal was identified for rhabdomyolysis in patients receiving ranolazine and statins.

Nine cases of drug interaction were related to concomitant use of ranolazine and a statin. Of those nine cases, seven (all male) involved the statin associated adverse events of rhabdomyolysis (6) and myalgia (1). Four of those six patients were stable on long-term statin therapy prior to the initiation of ranolazine. Most cases involved the use of simvastatin.

According to the OCP review:

> *Ranolazine and SV are both cleared via CYP3A metabolism. Hence, concomitant administration of the two may lead to pharmacokinetic DDI. Administration of ranolazine (1000 mg twice daily) with SV (80 mg once daily) resulted in a ~2-fold increase in C_{max} and ~1.5-fold increase in AUC of SV and SVA, at steady state. Increased systemic exposure to SV and SVA has been associated with increased risk of myopathy and rhabdomyolysis. The 80 mg dose of SV has been shown to be associated with increased incidence of myopathy and rhabdomyolysis. In addition, there is little gain in effectiveness of the 80 mg over 40 mg dose. The DMEP regulatory briefing held on 6/4/2010 suggested progressive removal of 80 mg dose of simvastatin from the market, leaving 40 mg as the highest available dose. Therefore, given the 2-fold increase in systemic exposure expected on concomitant administration of ranolazine and SV, limiting the dose of SV to 20 mg will avoid exposures similar or greater to that observed with 80 mg.*
>
> *In addition, for other statins which are primarily metabolized by CYP3A (e.g., lovastatin and atorvastatin), concomitant medications which are CYP3A inhibitors are expected to elevate statin exposure, and risk of myopathy. However, at present, definitive data (such as available with simvastatin) is not available for other statins, in order to recommend dose-adjustments.*

On June 8, 2011, in conjunction with the approval of new dosing restrictions with the 80 mg dose of simvastatin, DMEP approved a dose cap of simvastatin 20 mg when simvastatin is coadministered with ranolazine.

In addition, the current ranolazine label recommends a dose adjustment of sensitive CYP3A4 substrates such as lovastatin based on the 2-fold simvastatin exposure increase by ranolazine.

Based on the information above, the following recommendations for labeling changes were made:

Mevacor:

Under **WARNINGS**, ***Myopathy/Rhabdomyolysis***:

Ranolazine: The risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of ranolazine. Dose adjustment of lovastatin may be considered during co-administration.

Under **PRECAUTIONS,** *Other Drug Interactions*:

Ranolazine: The risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of ranolazine.

Altoprev:

Advicor:

6. Myopathy with concomitant administration with colchicine

In June 2010, a Regulatory Briefing was conducted to discuss the increased risk of myopathy, including rhabdomyolysis, associated with the use of simvastatin 80

mg, based on DMEP's review of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) clinical trial. In preparation for the briefing, OSE noted an interaction between statins and colchicine resulting in an increased risk of myopathy. Colchicine, a substrate of P-glycoprotein and CYP3A4, carried the following information in its label:

> **5.4 Neuromuscular Toxicity**
> Colchicine-induced neuromuscular toxicity and rhabdomyolysis have been reported with chronic treatment in therapeutic doses. Patients with renal dysfunction and elderly patients, even those with normal renal and hepatic function, are at increased risk. Concomitant use of atorvastatin, simvastatin, pravastatin, fluvastatin, gemfibrozil, fenofibrate, fenofibric acid, or benzafibrate (themselves associated with myotoxicity) or cyclosporine may potentiate the development of myopathy. Once colchicine is stopped, the symptoms generally resolve within 1 week to several months.

This was based on reports from the literature as summarized in the table below, and adapted from a 2008 OCP review of NDA 22-352 (Colstat [colchicine tablets]).

Lipid Lowering Agents			
HMG-CoA Reductase Inhibitors	Simvastatin: Baker *et al.* (2004); Hsu *et al.* (2002)	Both are CYP3A4 and P-gp substrates; P-gp inhibition by simvastatin	Acute myopathy or rhabdomyolysis (could be attributed to either drug)
	Fluvastatin: Atasoyu *et al.* (2005)	Synergistic myotoxicity *via* PK & PD mechanism; fluvastatin is not a P-gp inhibitor	
	Pravastatin: Alayli *et al.* (2005)	Synergistic myotoxicity *via* PK & PD mechanism; pravastatin is not a P-gp inhibitor	
	Atorvastatin: Tufan *et al.* (2006)	Both are CYP3A4 substrates; P-gp inhibition by atorvastatin	
Fibrates	Gemfibrozil; Atmaca *et al.*, 2002	Synergistic toxic effect of both drugs	
	Fenofibrate & Diltiazem: Sinsawaiwong *et al.*, 1997	Mechanism-based inhibition of CYP3A4 by diltiazem.	

On June 8, 2011, the following changes were approved for the simvastatin-containing drugs:

> **5 WARNINGS AND PRECAUTIONS**
> **5.1 Myopathy/Rhabdomyolysis**
> Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing simvastatin with colchicine.
>
> **7 DRUG INTERACTIONS**
> **7.7 Colchicine**
> Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing simvastatin with colchicine.

In order to harmonize and update the appropriate statin labels, similar labeling changes were requested for atorvastatin, pravastatin, and fluvastatin. Furthermore, because of physicochemical and pharmacokinetic similarities between lovastatin and simvastatin, similar labeling changes were requested for lovastatin.

7. Myopathy with concomitant administration with fibrates

A National Institutes of Health (NIH) funded trial, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial, was reviewed by DMEP and discussed at an Advisory Committee meeting on May 19, 2011. ACCORD-Lipid evaluated the occurrence of major adverse cardiovascular events (MACE), a composite of nonfatal heart attack, nonfatal stroke, and cardiovascular death in patients receiving simvastatin plus fenofibrate, compared to simvastatin alone. The trial found that there was no difference in cardiovascular outcomes between the two groups (Hazard Ratio = 0.92; 95% Confidence Interval: 0.79-1.08; p=0.32).

This was the second failed cardiovascular outcome trial for fenofibrate. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, fenofibrate demonstrated a non-significant 11% relative reduction in the primary outcome of coronary heart disease events (Hazard Ratio = 0.89; 95% Confidence Interval: 0.75-1.05; p=0.04) versus placebo.

The absence to date of proven cardiovascular benefit with fenofibrates must be viewed in the context of observational data showing an increase in the risk of myopathy with fenofibrates, especially when co-administered with a statin. In 2011, OSE conducted a review of observational data on rhabdomyolysis with fenofibrates and gemfibrozil in combination with statins. Their review looked at 3 studies:

- Graham DJ, Staffa JA, Shatin D et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-2590.
- Amend KL, Landon J, Thyagarajan V, Niemcryk S, McAfee A. Incidence of hospitalized rhabdomyolysis with statin and fibrate use in an insured US population. *Ann Pharmacother* 2011;45:1230-1239.
- Enger C, Gately R, Ming EE, Niemcryk SJ, Williams L, McAfee AT. Pharmacoepidemiology safety study of fibrate and statin concomitant therapy. *Am J Cardiol* 2010;106:1594-1601.

According to the OSE review, the best available evidence suggests that fenofibrate-statin combination is associated with an increased hazard rate for rhabdomyolysis (HR, 3.26, 95% CI, 1.21-8.80) relative to statin monotherapy. There also appears to be a differential risk associated with the gemfibrozil-statin combination therapy versus the fenofibrate-statin combination therapy, with a

numerically higher rate of rhabdomyolysis observed with gemfibrozil-statin combination therapy (HR, 11.93, 95% CI, 3.96-35.93) compared to statin monotherapy.

Most statin labels contain language in the FPI (Warnings and Precautions and Drug Interactions sections) regarding the increased risk of myopathy, including rhabdomyolysis, when statins and fibrates are co-administered. In order to highlight this increased risk, as well as to note the differential risk between gemfibrozil-statin combination therapy and fenofibrate-statin combination therapy, all sponsors of statin drugs with labels in the PLR format (i.e., all except the lovastatin products) were requested to add the following information to the Highlights page. The following language was also provided in the Drug Interactions section of the PI's, depending on the level of risk determined for each statin product:

----------DRUG INTERACTIONS----------

Other Lipid-lowering Medications: Use with other fibrate products or lipid-modifying doses (≥1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with <<STATIN>>.

7.X Lipid-Lowering Drugs That Can Cause Myopathy When Given Alone

Gemfibrozil: <<Contraindicated or Avoid>> with <<STATIN>>
Other fibrates: Caution should be used when prescribing with <<STATIN>>

7.X Gemfibrozil

Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are coadministered with gemfibrozil, concomitant administration of <<STATIN>> with gemfibrozil should be avoided.

7.X Other Fibrates

Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of other fibrates, <<STATIN>> should be administered with caution when used concomitantly with other fibrates.

8. Myopathy with concomitant administration with lipid-modifying doses of niacin

In March 2010, DMEP approved a labeling revision for simvastatin based on interim results from an ongoing clinical trial - the Heart Protection Study 2 (HPS2) – Treatment of HDL to Reduce the Incidence of Vascular Events (THRIVE), a cardiovascular outcome trial being conducted in 20,000 patients with vascular disease from the UK, China and Scandinavia to investigate whether combining niacin with a new drug (laropiprant) that minimizes niacin's flushing effect can reduce the risk of serious heart attacks and strokes among people already taking treatment to lower their LDL-cholesterol. The interim HPS2 – THRIVE results showed that the incidence of myopathy was higher in patients of

Chinese descent (0.43%) compared with patients not of Chinese descent (0.03%) taking 40 mg simvastatin plus cholesterol-modifying doses (≥1 g/day) of a niacin-containing product. The exact mechanism of this drug interaction is not fully understood.

Drug-drug interaction studies report an increase in simvastatin exposure of 41-64% with co-administration of simvastatin and ER niacin. According to OCP, the cause of the observed changes in exposure of simvastatin due to ER niacin is not well established as this is not due to changes in the known pathways (e.g., via CYP3A4 or OATP1B1). Furthermore, a PK study of simvastatin in Chinese subjects showed no significant differences in Chinese and non-Asian subjects in simvastatin C_{max} and $AUC_{0\text{-last}}$, and simvastatin acid $AUC_{0\text{-last}}$ or C_{max}.

The OCP Genomics Group further noted that the SLCO1B1 genotype that has been associated with statin-induced myopathy, is less prevalent in Asian populations than European populations and, therefore, does not seem to explain the higher myopathy risk rates among Chinese subjects in HPS2-THRIVE.

So, it remains unclear if this increased risk of myopathy with statin and niacin co-administration is unique to Chinese subjects, or applies to other Asians and non-Asians as well.

Furthermore, in the AIM-HIGH study, which compared ER-niacin with simvastatin to simvastatin alone in reducing the residual cardiovascular risk in patients with established cardiovascular disease, "there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36-month follow-up period, despite significant improvements in HDL cholesterol and triglyceride levels".

The lack of clear benefit in conjunction with uncertainty as to the nature of the increased risk of myopathy in patients treated with niacin plus a statin led FDA to believe that this risk needed to be highlighted in statin labeling.

The labeling approved for simvastatin in March 2010 noted that patients of Chinese descent should not receive simvastatin 80 mg with cholesterol-modifying doses of niacin-containing products.

In June 2011, in conjunction with labeling revisions required based on the Agency's review of the SEARCH trial, this language was modified to note that "caution should be used when treating Chinese patients with simvastatin doses exceeding 20 mg/day coadministered with lipid-modifying doses of niacin-containing products."

Most statin labels contain information in the FPI (Warnings and Precautions and Drug Interactions sections) noting that "The risk of skeletal muscle effects may be enhanced when <<STATIN>> is used in combination with niacin; a reduction in

<<STATIN>> dosage should be considered in this setting." All sponsors of statin drugs with labels in the PLR format were requested to modify the HIGHLIGHTS page, with corresponding changes to the FPI if indicated, as follows:

----------DRUG INTERACTIONS----------

Other Lipid-lowering Medications: Use with other fibrate products or lipid-modifying doses (≥1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with <<STATIN>>.

7.X Niacin

The risk of skeletal muscle effects may be enhanced when <<STATIN>> is used in combination with lipid-modifying doses (≥1 g/day) of niacin; a reduction in <<STATIN>> dosage should be considered in this setting.

9. Update to lovastatin drug-drug interactions and dose caps

Subsequent to the June 2011 labeling revisions to the simvastatin-containing products which were largely based on the SEARCH clinical trial data and the increased risk of myopathy associated with the 80 mg dose of simvastatin, a review of drug-drug interactions with lovastatin was conducted. The physicochemical and pharmacokinetic properties of lovastatin are comparable with those of simvastatin. Lovastatin is a sensitive *in vivo* CYP3A4 substrate; therefore, strong CYP3A4 inhibitors are predicted to significantly increase lovastatin exposure. According to OCP:

> *Itraconazole increased the exposure of lovastatin (up to 20-fold) more than that of simvastatin (up to 13-fold), and it indicates that strong CYP3A4 inhibitor can cause greater lovastatin exposure increase compared to that of simvastatin. Therefore, it seems reasonable to extrapolate the effect of strong CYP3A4 inhibitors on simvastatin to that on lovastatin.*

Based on available studies from the literature, as well as extrapolation from simvastatin data, the following changes to the lovastatin label were recommended:

Under **CONTRAINDICATIONS:**

> Concomitant administration with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone).

Under **WARNINGS, *Myopathy/Rhabdomyolysis*, Strong ~~Potent~~ inhibitors of CYP3A4:**

> Lovastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of cytochrome P450 3A4 (CYP3A4). ~~When lovastatin is used with a potent inhibitor of~~

~~CYP3A4, elevated plasma levels of HMG-CoA reductase inhibitory activity can increase the risk of myopathy and rhabdomyolysis, particularly with higher doses of lovastatin.~~ Certain drugs which inhibit this metabolic pathway can raise the plasma levels of lovastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, and posaconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, boceprevir, telaprevir, or the antidepressant nefazodone. Combination of these drugs with lovastatin is contraindicated.

~~The use of lovastatin concomitantly with the potent CYP3A4 inhibitors itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) should be avoided.~~ ~~Concomitant use of other medicines labeled as having a potent strong inhibitory effect on CYP3A4 should be avoided unless the benefits of combined therapy outweigh the increased risk.~~ If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with lovastatin should be suspended during the course of treatment.

Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentration of lovastatin. It is recommended that dose adjustment of lovastatin be considered during coadministration. Increased lovastatin concentration in plasma has been associated with an increased risk of myopathy/rhabdomyolysis.

Under **WARNINGS,** ***Myopathy/Rhabdomyolysis:***

Gemfibrozil~~, particularly with higher doses of lovastatin: The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with gemfibrozil.~~ The combined use of lovastatin with gemfibrozil should be avoided~~, unless the benefits are likely to outweigh the increased risks of this drug combination~~.

Other lipid-lowering drugs (other fibrates or ≥1 g/day of niacin): ~~The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with other fibrates or ≥1 g/day of niacin.~~ Caution should be used when prescribing other fibrates or lipid-lowering doses (≥1 g/day) of niacin with lovastatin, as these agents can cause myopathy when given alone. **The benefit of further alterations in lipid levels by the combined use of lovastatin with other fibrates or niacin should be carefully weighed against the potential risks of these combinations.**

Cyclosporine: The use of lovastatin with cyclosporine should be avoided.

~~Cyclosporine or d~~Danazol, diltiazem or verapamil with higher doses of lovastatin: The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with ~~cyclosporine or~~ danazol, diltiazem, or verapamil. The benefits of the use of lovastatin in patients receiving ~~cyclosporine or~~ danazol, diltiazem, or verapamil should be carefully weighed against the risks of these combinations.

Amiodarone~~ or verapamil~~: The dose of lovastatin should not exceed 40 mg daily in patients receiving concomitant medication with amiodarone ~~or verapamil~~. The combined use of lovastatin at doses higher than 40 mg daily with amiodarone~~ or verapamil~~ should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy. The risk of myopathy/rhabdomyolysis is

increased when ~~either~~ amiodarone ~~or verapamil~~ is used concomitantly with higher doses of a closely related member of the HMG-CoA reductase inhibitor class.

Under **WARNINGS**, ***Myopathy/Rhabdomyolysis:***

Cyclosporine: The use of lovastatin with cyclosporine should be avoided.

Amiodarone ~~or verapamil~~: The dose of lovastatin should not exceed 40 mg daily in patients receiving concomitant medication with amiodarone ~~or verapamil~~. The combined use of lovastatin at doses higher than 40 mg daily with amiodarone ~~or verapamil~~ should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy. The risk of myopathy/rhabdomyolysis is increased when ~~either~~ amiodarone ~~or verapamil~~ is used concomitantly with higher doses of a closely related member of the HMG-CoA reductase inhibitor class.

~~Cyclosporine, or d~~Danazol, diltiazem or verapamil with higher doses of lovastatin: The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with ~~cyclosporine, or~~ danazol, diltiazem, or verapamil. The benefits of the use of lovastatin in patient receiving ~~cyclosporine, or~~ danazol, diltiazem, or verapamil should be carefully weighed against the risks of these combinations.

Under **WARNINGS,** ***Myopathy/Rhabdomyolysis,*** Table VII: Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis**:**

Interacting Agents	**Prescribing Recommendations**
Ketoconazole Itraconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Boceprevir Telaprevir Nefazodone	~~Avoid~~ Contraindicated with lovastatin
Gemfibrozil Cyclosporine	Avoid with lovastatin
~~Gembibrozil~~ ~~Other fibrates~~ ~~Lipid-lowering doses (≥1 g/day) of nicacin~~ ~~Cyclosporine~~ Danazol Diltiazem Verapamil	Do not exceed 20 mg lovastatin daily
Amiodarone ~~Verapamil~~	Do not exceed 40 mg lovastatin daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

Under **PRECAUTIONS**, *Drug Interactions, CYP3A4 Interactions*:

Lovastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. ~~Potent~~ Strong inhibitors of CYP3A4 (e.g., ~~below~~ itraconazole, ketoconazole, posaconazole, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone and erythromycin), and large quantities of grapefruit juice increase the risk of myopathy by reducing the elimination of lovastatin

~~**Itraconazole**~~
~~**Ketoconazole**~~
~~**Erythromycin**~~
~~**Clarithromycin**~~
~~**Telithromycin**~~
~~**HIV protease inhibitors**~~
~~**Nefazodone**~~
~~**Large quantities of grapefruit juice (>1 quart daily)**~~

In vitro studies have demonstrated that voriconazole inhibits the metabolism of lovastatin. Adjustment of the lovastatin dose may be needed to reduce the risk of myopathy, including rhabdomyolysis, if voriconazole must be used concomitantly with lovastatin.

Under **PRECAUTIONS**, *Other Drug Interactions:*

Cyclosporine ~~or Danazol~~: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine ~~or danazol particularly with higher doses of lovastatin~~.

Danazol, Diltiazem, or Verapamil: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of danazol, diltiazem, or verapamil particularly with higher doses of lovastatin.

Amiodarone ~~or Verapamil~~: The risk of myopathy/rhabdomyolysis is increased when either amiodarone ~~or verapamil~~ is used concomitantly with a closely related member of the HMG-CoA reductase inhibitor class.

Under **PRECAUTIONS,** *Endocrine Function*:

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.

Under **DOSAGE AND ADMINISTRATION:**

Dosage in Patients taking ~~Cyclosporine, or~~ Danazol, Diltiazem, or Verapamil
In patients taking ~~cyclosporine, or~~ danazol, diltiazem, or verapamil concomitantly with lovastatin, therapy should begin with 10 mg of lovastatin and should not exceed 20 mg/day.

Dosage in Patients taking Amiodarone ~~or Verapamil~~
In patients taking amiodarone ~~or verapamil~~ concomitantly with MEVACOR, the dose should not exceed 40 mg/day.

Concomitant Lipid-Lowering Therapy
MEVACOR is effective alone or when used concomitantly with bile-acid sequestrants. ~~If MEVACOR is used in combination with gemfibrozil, other fibrates or lipid-lowering doses (≥ 1g/day) of niacin, the dose of MEVACOR should not exceed 20 mg/day~~.

Under **CLINICAL PHARMACOLOGY**:

	Number of Subjects	Dosing of Coadministered Drug or Grapefruit Juice	Dosing of Lovastatin	AUC Ratio* (with / without coadministered drug) No Effect = 1.00	
				Lovastatin	Lovastatin acid†
Gemfibrozil	11	600 mg BID for 3 days	40 mg	0 96	2 80
Itraconazole‡	12	200 mg QD for 4 days	40 mg on Day 4	> 36§	22
	10	100 mg QD for 4 days	40 mg on Day 4	> 14 8§	15 4
Grapefruit Juice¶ (high dose)	10	200 mL of double-strength TID#	80 mg single dose	15.3	5.0
Grapefruit Juice¶ (low dose)	16	8 oz (about 250 mL) of single-strengthÞ for 4 days	40 mg single dose	1.94	1.57
Cyclosporine	16	Not describedß	10 mg QD for 10 days	5- to 8-fold	NDà
	Number of Subjects	**Dosing of Coadministered Drug or Grapefruit Juice**	**Dosing of Lovastatin**	**AUC Ratio* (with / without coadministered drug) No Effect = 1.00**	
				Total Lovastatin acide	
Diltiazem	10	120 mg BID for 14 days	20 mg	3 57è	

* Results based on a chemical assay

† Lovastatin acid refers to the β-hydroxyacid of lovastatin

‡ The mean total AUC of lovastatin without itraconazole phase could not be determined accurately Results could be representative of strong CYP3A4 inhibitors such as ketoconazole, posaconazole, clarithromycin, telithromycin, HIV protease inhibitors, and nefazodone

§ Estimated minimum change

¶ The effect of amounts of grapefruit juice between those used in these two studies on lovastatin pharmacokinetics has not been studied

Double-strength: one can of frozen concentrate diluted with one can of water Grapefruit juice was administered TID for 2 days, and 200 mL together with single dose lovastatin and 30 and 90 minutes following single dose lovastatin on Day 3

Þ Single-strength: one can of frozen concentrate diluted with 3 cans of water Grapefruit juice was administered with breakfast for 3 days, and lovastatin was administered in the evening on Day 3

ß Cyclosporine-treated patients with psoriasis or post kidney or heart transplant patients with stable graft function, transplanted at least 9 months prior to study

10. Update to simvastatin and lovastatin drug-drug interaction:

In May 2011, the hepatitis C protease inhibitors boceprevir and telaprevir were approved. These protease inhibitors have been characterized as being strong CYP3A4 inhibitors. Because simvastatin is contraindicated with strong CYP3A4 inhibitors, and because the simvastatin label individually lists strong CYP3A4 inhibitors with which simvastatin is contraindicated, these two recently approved protease inhibitors will be added to the list in all simvastatin-containing products (Zocor, Vytorin, and Simcor).

Because of the physicochemical and pharmacokinetic similarities between simvastatin and lovastatin, and consistent with changes being made to the lovastatin labeling which include a new contraindication with strong CYP3A4 inhibitors, the labeling for lovastatin will be modified to add boceprevir and telaprevir to the list of strong CYP3A4 inhibitors with which lovastatin is contraindicated.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY G EGAN
02/27/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019643Orig1s085

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Memo to File

NDA #:	19643
Sponsor:	Merck
Drug:	Mevacor (Lovastatin)
Memo Date:	10/11/2011; 10/28/2011
Reviewer:	Sang M. Chung, Ph.D.
Team Leader:	Jayabharathi Vaidyanathan, Ph.D. (Acting)
RE:	PAS Request on August 11, 2011

The Agency requested the sponsor to submit a Prior Approval Supplement (PAS) (see the Attachment) as part of the statin class labeling update. The sponsor requested for clarification of rationale related to the change of ketoconazole from a warning to a contraindication. The purpose of this memorandum is to address the clarification requested from sponsor as well as to review the label information that was submitted in response to the supplement request letter.

Reviewer's Comment:

1. Strong CYP3A4 Inhibitors: Available data support a contraindication not only for ketoconazole but also other strong CYP3A4 inhibitors to lovastatin as follows. In those regards, ketoconazole should have been suggested for contraindication as an example of strong CYP3A4 inhibitors.

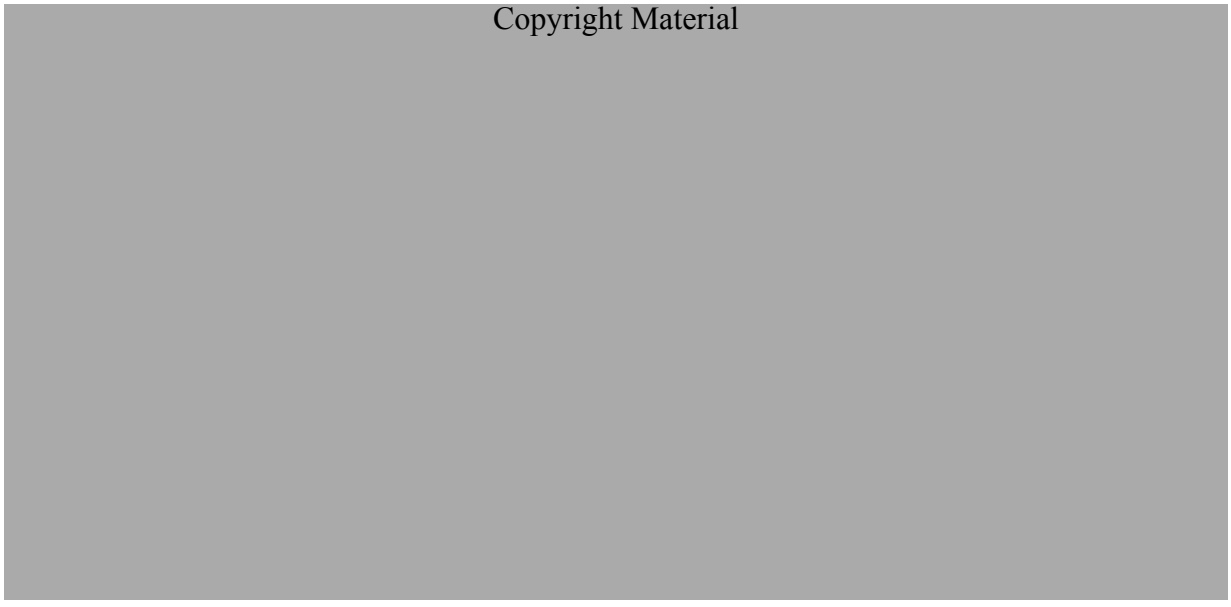
- According to the Guidance for Industry Drug Interaction Studies, lovastatin is listed as one of the sensitive in vivo CYP3A4 substrates. Therefore, strong CYP3A4 inhibitors are predicted to significantly increase lovastatin exposure because lovastatin is extensively metabolized by CYP3A4 isozyme (1).
- Literature survey indicates that itraconazole increases lovastatin exposure up to 15-20-fold (2, 3) and the drug interaction seems to result in rhabdomyolysis (4). Itraconazole is the representative strong CYP3A4 inhibitor and therefore, the effect of itraconazole on lovastatin exposure can be extrapolated to other strong CYP3A4 inhibitors listed in the Guidance (1) as well as the FDA website (5).
- Strong CYP3A4 inhibitors are contraindicated for simvastatin because of the significant drug interaction and its potential for the increased risk on the rhabdomyolysis. Physicochemical and pharmacokinetic properties of lovastatin are comparable with those of simvastatin. Meanwhile, itraconazole increased the exposure of lovastatin (up to 20-fold) more than that of simvastatin (up to 13-fold), and it indicates that strong CYP3A4 inhibitor can cause greater lovastatin exposure increase compared to that of simvastatin. Therefore, it seems reasonable to extrapolate the effect of strong CYP3A4 inhibitors on simvastatin to that on lovastatin.

- The drug interaction results with cyclosporine or itraconazole are highly dependent on study design such as dose. In addition, drug interaction studies with cyclosporine are often confounded with many other underline therapies such as other immunosuppresants unless a study is conducted with healthy volunteers. Therefore, there should be caution on a cross study comparison among literature information. There are numerous additional reports for the effect of itraconazole or cyclosporine on lovastatin exposure as follows. Merck should further evaluate those for Table 1 in Mevacor labeling.

    - Cyclosporine and lovastatin
        - Transplant Proc. 1999 Aug;31(5):2163-5, Interaction between lovastatin and cyclosporine A after heart and kidney transplantation.
        - Clin Pharmacol Ther. 1997 Sep;62(3):311-21, Accumulation of lovastatin, but not pravastatin, in the blood of cyclosporine-treated kidney graft patients after multiple doses.
        - Nephron. 1993;65(3):410-3, Plasma concentration profiles of simvastatin 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitory activity in kidney transplant recipients with and without ciclosporin.
    - Itraconazole and lovastatin (same as reference 2 and 3)
        - Clin Pharmacol Ther. 60(1):54-61, Itraconazole drastically increases plasma concentrations of lovastatin and lovastatin acid
        - Br J Clin Pharmacol. 46(1):49-53, Different effects of itraconazole on the pharmacokinetics of fluvastatin and lovastatin.

2. Erythromycin: Although erythromycin is a moderate CYP3A4 inhibitor, it is contraindicated for simvastatin because it significantly increased simvastatin exposure (e.g., simvastatin AUC increase up to 6-fold as shown in the following table) and there were rhabodomyolysis case reports for co-administration of simvastatin and erythromycin (7, 8).

Simvastatin and simvastatin acid pharmacokinetics following co-administration of 40 mg simvastatin + 1.5 g/day erythromycin (500 mg TID) or 240 mg/day verapamil (80 mg TID) for 2 days in 12 healthy subjects (data from reference 6)



For lovastatin, the pharmacokinetic study evaluating the effect of erythromycin on lovastatin is not available in literature. However, there were rhabodomyolysis case reports for co-administration of lovastatin and erythromycin (9, 10). In addition, erythromycin is expected to increase lovastatin exposure comparable to its effect on simvastatin because both lovastatin and simvastatin are sensitive CYP3A4 substrates. Among known moderate CYP3A4 inhibitors, the effect of diltiazem is available for both lovastatin and simvastatin in literature as follows and those data support that a moderate CYP3A4 inhibitor can increase lovastatin exposure comparable to its effect on simvastatin exposure:

- AUC and Cmax of lovastatin+lovastatin acid following lovastatin 20 mg were increased to 4.1-fold (range of 1.51 to 10.1-fold) and 4.7-fold (range of 2.6 to 7.2-fold), respectively, following 120 mg diltiazem BID for 2 weeks (11).
- AUC and Cmax of simvastatin following 20 mg simvastatin were increased by 4.6- and 3.6-fold, respectively, following diltiazem 120 mg BID for 14 days (Zocor labeling).

Therefore, it seems reasonable to extrapolate the effect of erythromycin on simvastatin to that on lovastatin. Hence, erythromycin should also be contraindicated with lovastatin.

3. Colchicine: According to the clinical pharmacology review of the original NDA for colchicine, there was no metabolic inhibition potential of colchicine on CYP3A4 (refer the review by Dr. Srikanth Nallani on NDA 22352 in DARRTS dated 11/26/2008 for Colstat). It seems that the caution on atorvastatin, simvastatin, pravastatin, and fluvastatin in colchicine labeling is based on the adverse events such as case reports on myopathy. Therefore, there is no pharmacokinetic data to support the caution on colchicine for lovastatin and the Agency's recommendation is based on an extrapolation from colchicine and simvastatin adverse event data.

4. Ranolazine: Merck's proposal seems reasonable according to the ranolazine labeling. Ranolazine labeling recommends a dose adjustment of other sensitive CYP3A4 substrates such as lovastatin based on the two-fold simvastatin exposure increase by ranolazine.

> Merck's proposal: <u>Dose adjustment of lovastatin may be considered during co-administration with ranolazine.</u>

Ranolazine labeling related to CYP3A4:

7.2 Effects of Ranolazine on Other Drugs
Drugs Metabolized by CYP3A
Limit the dose of simvastatin in patients on any dose of Ranexa to 20 mg once daily, when ranolazine is co-administered. Dose adjustment of other sensitive CYP3A substrates (e.g., lovastatin) and CYP3A substrates with a narrow therapeutic range (e.g., cyclosporine, tacrolimus, sirolimus) may be required as Ranexa may increase plasma concentrations of these drugs *[see Clinical Pharmacology (12.3)]*.

12.3 Pharmacokinetics
Effect of ranolazine on other drugs

In vitro ranolazine and its O-demethylated metabolite are weak inhibitors of CYP3A and moderate inhibitors of CYP2D6 and P-gp. *In vitro* ranolazine is an inhibitor of OCT2.

Recommendation:

- Contraindication
    - It is recommended to change the lovastatin labeling language for ketoconazole as well as all other strong CYP3A inhibitors (as listed in the FDA guidance and FDA website (1, 5) from warning/avoid to contraindicate.
    - It is recommended to change erythromycin from 'avoid' to 'contraindication'.
- Diltiazem: It is recommended a dosing cap for lovastatin 20 mg with diltiazem because of 4.1-fold lovastatin AUC increase by diltiazem.
- Verapamil: It is recommended a dosing cap for lovastatin from 40 mg to 20 mg with verapamil as an extrapolation of simvastatin data.
- Colchicine: The recommend caution labeling by the Agency seems reasonable as an extrapolation from simvastatin AE data.
- Ranolazine: Merck's proposal seems reasonable.
- Table 1: Merck should add additional data related to itraconazole.

Labeling Comments

- ~~Strikethrough~~ text indicates deletion and red text indicates addition.
- The following comment is based on the Merck's submission on 10/28/2011

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1. Under **CLINICAL PHARMACOLOGY**:

Modify Table 1 as follows:

	Number of Subjects	Dosing of Coadministered Drug or Grapefruit Juice	Dosing of Lovastatin	AUC Ratio* (with / without coadministered drug) No Effect = 1.00	
				Lovastatin	Lovastatin acid†
Itraconazole‡	12	200 mg QD for 4 days	40 mg on Day 4	> 36§	22
	10	100 mg QD for 4 days	40 mg on Day 4	> 14 8§	15 4

‡ The mean total AUC of lovastatin without itraconazole phase could not be determined accurately _Results could be representative of ~~the following~~ strong_CYP3A4 inhibitors~~:~~ such as_ketoconazole, posaconazole, ~~erythromycin,~~ clarithromycin, telithromycin, HIV protease inhibitors, and nefazodone

2. Under **CONTRAINDICATIONS:**

Replace ketoconazole with strong CYP3A4 inhibitors:

Concomitant use with ~~ketoconazole~~ strong CYP3A4 inhibitors.

3. Under **WARNINGS**, ***Myopathy/Rhabdomyolysis***,

Modify as follows:

The risk of myopathy/rhabdomyolysis is increased by concomitant use of lovastatin with the following:

Strong inhibitors of CYP3A4: Lovastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of cytochrome P450 3A4 (CYP3A4). ~~When lovastatin is used with a strong inhibitor of CYP3A4, elevated plasma levels of HMG-CoA reductase inhibitory activity can increase the risk of myopathy and rhabdomyolysis, particularly with higher doses of lovastatin.~~ Certain drugs which inhibit this metabolic pathway can raise the plasma levels of lovastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, and posaconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, or the antidepressant nefazodone. Combination of these drugs with lovastatin is contraindicated. In addition, grapefruit juice should be avoided with lovastatin

(b) (4)

~~**Due to the increased risk of myopathy/rhabdomyolysis the concomitant use of lovastatin with ketoconazole is contraindicated.**~~

~~**The use of lovastatin concomitantly with the potent strong CYP3A4 inhibitors itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) should be avoided.** Concomitant use of other medicines labeled as having a strong inhibitory effect on CYP3A4 should be avoided unless the benefits of combined therapy outweigh the increased risk.~~ If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with lovastatin should be suspended during the course of treatment.

4. Under **WARNINGS**, ***Myopathy/Rhabdomyolysis***:

   Add as a separate paragraph after the paragraph on **Amiodarone or verapamil:**

   Colchicine*:* Cases of myopathy, including rhabdomyolysis, have been reported with a statin similar to lovastatin coadministered with colchicine, and caution should be exercised when prescribing lovastatin with colchicine.

5. Under **WARNINGS, *Myopathy/Rhabdomyolysis,*** Table VII: Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis**:**

   Modify as follows:

Interacting Agents	**Prescribing Recommendations**
Ketoconazole Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone	~~Avoid~~ Contraindicated with lovastatin
Gemfibrozil Other fibrates Lipid-lowering doses (≥1 g/day) of niacin Cyclosporine Danazol Diltiazem Verapamil	Do not exceed 20 mg lovastatin daily
Amiodarone ~~Verapamil~~	Do not exceed 40 mg lovastatin daily
Grapefruit juice	Avoid ~~large quantities of grapefruit juice (>1 quart daily)~~

6. Under **PRECAUTIONS**, *Drug Interactions, CYP3A4 Interactions*:

Modify as follows:

Lovastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Strong inhibitors of CYP3A4 (e.g., ~~below~~ itraconazole, ketoconazole, posaconazole, clarithromycin, telithromycin, HIV protease inhibitors, and nefazodone), erythromycin, and grapefruit juice increase the risk of myopathy by reducing the elimination of lovastatin **(See WARNINGS, *Myopathy/Rhabdomyolysis*, and CLINICAL PHARMACOLOGY, *Pharmacokinetics*).**

~~**Itraconazole**~~
~~**Ketoconazole**~~
~~**Erythromycin**~~
~~**Clarithromycin**~~
~~**Telithromycin**~~
~~**HIV protease inhibitors**~~
~~**Nefazodone**~~
~~**Large quantities of grapefruit juice (>1 quart daily)**~~

Reference

1. Guidance for Industry Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072101.pdf)
2. Neuvonen PJ, Jalava KM, Itraconazole drastically increases plasma concentrations of lovastatin and lovastatin acid, Clin Pharmacol Ther. 60(1):54-61 (1996)
3. Kivistö KT, Kantola T, Neuvonen PJ. Different effects of itraconazole on the pharmacokinetics of fluvastatin and lovastatin. Br J Clin Pharmacol. 46(1):49-53 (1998)
4. Lees RS, Lees AM Rhabdomyolysis from the coadministration of lovastatin and the antifungal agent itraconazole, N Engl J Med. 333(10):664-5 (1995)
5. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers at the FDA website (link: http://wcms.fda.gov/FDAgov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm)
6. Knatola T, Kivisto KT, Neuvonen PJ, Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. Clin Pharmacol Ther 64:177-82 (1998)
7. Molden E, Andersson KS, Simvastatin-associated rhabdomyolysis after coadministration of macrolide antibiotics in two patients, Pharmacotherapy. 27(4):603-7 (2007)
8. Campbell G, Jayakumar U, McCracken S, Bene J. A cautionary tale: delayed onset rhabdomyolysis due to erythromycin/simvastatin interaction. Age Ageing. 36(5):597 (2007)
9. Wong PW, Dillard TA, Kroenke K. Multiple organ toxicity from addition of erythromycin to long-term lovastatin therapy. South Med J. 91(2):202-5 (1998)
10. Spach DH, Bauwens JE, Clark CD, Burke WG. Rhabdomyolysis associated with lovastatin and erythromycin use. West J Med. Feb;154(2):213-5 (1991)
11. Azie NE, Brater DC, Becker PA, Jones DR, Hall SD. The interaction of diltiazem with lovastatin and pravastatin. Clin Pharmacol Ther. 1998 Oct;64(4):369-77

Attachment starts here.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 19643

PRIOR APPROVAL SUPPLEMENT REQUEST

Merck Sharp & Dohme Corp.
Attention: David R. Hobart, Ph.D.
Manager, Worldwide Regulatory Affairs
P.O. Box 2000, RY 33-208
Rahway NJ 07065-0900

Dear Dr. Hobart:

Please refer to your new drug application (NDA) for Mevacor (lovastatin) Tablets 20 mg and 40 mg.

FDA has completed a comprehensive review of the HMG-CoA reductase inhibitor (statin) class of drugs, including clinical trial data, Adverse Event Reporting System (AERS) reports, the published literature, and the labels of other approved drugs containing information on statin co-administration. Based on the results of our review, you are requested to modify the Prescribing Information (PI) for Mevacor.

We request that the following changes in the labeling be made so as to furnish adequate information for the safe and effective use of the drug:

Under **ADVERSE REACTIONS,** *Neurological*:

Delete:

~~memory loss~~

and add the following new paragraph:

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Under **WARNINGS,** ***Myopathy/Rhabdomyolysis***:

Delete the last sentence in the 4th paragraph:

~~Therapy with lovastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.~~

and replace it with:

MEVACOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. MEVACOR therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.

Under **PRECAUTIONS,** *Endocrine Function*:

Add the following first paragraph:

Increases in HbA1c and fasting serum glucose levels have been reported with other HMG-CoA reductase inhibitors. There are insufficient data for MEVACOR to make a determination regarding this risk.

Under **WARNINGS**, ***Myopathy/Rhabdomyolysis***,

Modify as follows:

~~**Potent**~~ **Strong inhibitors of CYP3A4**:

and add the following last paragraph:

Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentration of lovastatin. It is recommended that dose adjustment of lovastatin be considered during coadministration. Increased lovastatin concentration in plasma has been associated with rhabdomyolysis.

Under **PRECAUTIONS**, *Drug Interactions, CYP3A4 Interactions*:

Add the following last paragraph:
In vitro studies have demonstrated that voriconazole inhibits the metabolism of lovastatin. Adjustment of the lovastatin dose may be needed to reduce the risk of myopathy, including rhabdomyolysis, if voriconazole must be used concomitantly with lovastatin.

Under **CONTRAINDICATIONS:**

Add:

Concomitant use with ketoconazole.

Under **WARNINGS, *Myopathy/Rhabdomyolysis*, ~~Potent~~ Strong inhibitors of CYP3A4:**

Modify the second sentence of the first paragraph as follows:

When lovastatin is used with a ~~potent~~ strong inhibitor of CYP3A4, elevated plasma levels of HMG-CoA reductase inhibitory activity can increase the risk of myopathy and rhabdomyolysis, particularly with higher doses of lovastatin.

and modify the 2nd paragraph as follows:

The use of lovastatin concomitantly with the ~~potent~~ strong CYP3A4 inhibitors itraconazole, ~~ketoconazole~~, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) should be avoided. Concomitant use of other medicines labeled as having a ~~potent~~ strong inhibitory effect on CYP3A4 should be avoided unless the benefits of combined therapy outweigh the increased risk.

and add above it as a separate paragraph:

Due to the increased risk of myopathy/rhabdomyolysis the concomitant use of lovastatin with ketoconazole is contraindicated.

Under **WARNINGS,** ***Myopathy/Rhabdomyolysis,*** Table VI: Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis:

Modify as follows:

Interacting Agents	Prescribing Recommendations
Ketoconazole	Contraindicated with lovastatin
Itraconazole ~~Ketoconazole~~ Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone	Avoid lovastatin
Gemfibrozil Other fibrates Lipid-lowering doses (≥1 g/day) of niacin Cyclosporine Danazol	Do not exceed 20 mg lovastatin daily
Amiodarone Verapamil	Do not exceed 40 mg lovastatin daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

Under **PRECAUTIONS,** *Endocrine Function*:

Modify the last sentence as follows:

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.

Under **WARNINGS**, ***Myopathy/Rhabdomyolysis***, **~~Potent~~ Strong inhibitors of CYPP3A4:**

Add the following beneath the new voriconazole paragraph:

Although not studied clinically with lovastatin, posaconazole may increase the plasma concentrations of statins that are metabolized by CYP3A4, such as lovastatin. Increased plasma lovastatin concentrations are associated with rhabdomyolysis. It is recommended that patients be monitored for adverse events and dose reduction of lovastatin be considered during co-administration with posaconazole.

Under **PRECAUTIONS,** *Drug Interactions, CYP3A4 Interactions*:

Add as a last paragraph under the new voriconazole paragraph:

Clinical studies with simvastatin suggest that posaconazole may increase the plasma concentrations of lovastatin. Adjustment of the lovastatin dose may be needed to reduce the risk of myopathy, including rhabdomyolysis, if posaconazole must be used concomitantly with lovastatin.

Under **WARNINGS**, ***Myopathy/Rhabdomyolysis***:

Add as a separate paragraph after the paragraph on **Amiodarone or verapamil:**

Colchicine: Cases of myopathy, including rhabdomyolysis, have been reported with lovastatin coadministered with colchicine, and caution should be exercised when prescribing lovastatin with colchicine.

Under **PRECAUTIONS**, *Other Drug Interactions*:

Add as a separate section under *Coumarin Anticoagulants*:

Colchicine: Cases of myopathy, including rhabdomyolysis, have been reported with lovastatin coadministered with colchicine, and caution should be exercised when prescribing lovastatin with colchicine.

Under **WARNINGS**, ***Myopathy/Rhabdomyolysis***:

Add as a separate paragraph under the new colchicine paragraph:

Ranolazine: The risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of ranolazine. Caution should be exercised when prescribing lovastatin with ranolazine.

Under **PRECAUTIONS**, *Other Drug Interactions*:

Add as a separate section under the new *Colchicine* section:

Ranolazine: The risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of ranolazine. Caution should be exercised when prescribing lovastatin with ranolazine.

Under **WARNINGS**, *Liver Dysfunction:*

Delete:

~~It is recommended that liver function tests be performed prior to initiation of therapy in patients with a history of liver disease, or when otherwise clinically indicated. It is recommended that liver function tests be performed in all patients prior to use of 40 mg or more daily and thereafter when clinically indicated. 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) returns 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.~~

and replace it with:

It is recommended that liver enzyme tests be obtained prior to initiating therapy with MEVACOR and repeated as clinically indicated.

There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including lovastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with MEVACOR, promptly interrupt therapy. If an alternate etiology is not found do not restart MEVACOR.

Under **ADVERSE REACTIONS,** *Gastrointestinal*:

Add:

fatal and non-fatal hepatic failure

Under **PRECAUTIONS,** ***Information for Patients*:**

Add a new section before *Endocrine Function*:

Liver Dysfunction
It is recommended that liver enzymes be checked before starting therapy, and if signs or symptoms of liver injury occur. All patients treated with MEVACOR should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.

Under **CLINICAL PHARMACOLOGY,** *Pharmacokinetics:*

Modify the first sentence of the first paragraph as follows:

Lovastatin is a lactone which is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid, a ~~potent~~ strong inhibitor of HMG-CoA reductase.

and the second sentence of the eighth paragraph as follows:

~~Potent~~ Strong inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*).

Under **PRECAUTIONS**, *Drug Interactions, CYP3A4 Interactions*:

Modify the second sentence of the first paragraph as follows:

~~Potent~~ Strong inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of lovastatin.

Under **PRECAUTIONS**, *Drug Interactions, Interactions With Lipid-Lowering Drugs That Can Cause Myopathy When Given Alone*:

Modify the first sentence of the first paragraph as follows:

The risk of myopathy is also increased by the following lipid-lowering drugs that are not ~~potent~~ strong CYP3A4 inhibitors, but which can cause myopathy when given alone.

Under **CLINICAL PHARMACOLOGY,** *Pharmacokinetics:*

Please provide current drug-drug interaction information in a tabular format (see below) using the published literature and your in-house data:

TABLE The Effect of Other Drugs on Lovastatin Exposure When Both Were Co-administered

	Number of Subjects	Dosing of Co-administered Drug or Grapefruit Juice	Dosing of Lovastatin	AUC Ratio[1] (with / without co-administered drug) No Effect = 1.00	
				Lovastatin	Lovastatin acid
Cyclosporine					
Diltiazem					
Gemfibrozil					
Itraconazole					
Nefazodone					
Grapefruit Juice (high dose)					
Grapefruit Juice (low dose)					

Submit draft labeling as a prior approval supplement to this application, incorporating all revisions since the last approval of the package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. Your supplement must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Please submit this prior approval labeling supplement by October 30, 2011.

If you have any questions, call Margaret Simoneau, M.S., RPh., Regulatory Project Manager, at (301) 796-1295.

Sincerely,

{See appended electronic signature page}

Amy G. Egan, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

AMY G EGAN
08/11/2011

Reference ID: 2999610

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/s/

SANG M CHUNG
12/06/2011

JAYABHARATHI VAIDYANATHAN
12/06/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019643Orig1s085

OTHER REVIEW(S)

Division of Metabolic & Endocrine Drug Products

Labeling Review

Application Number: 19-643/S-085

Name of Drug: Mevacor (lovastatin)Tablets

Sponsor: Merck

Submission Date: October 28, 2011 and final PI: February 23, 2012 (email)

Background and Summary:

Mevacor is indicated in the *Primary Prevention of Coronary Heart Disease, Coronary Heart Disease, Hypercholesterolemia and Adolescent Patients with Heterozygous Familial Hypercholesterolemia.* It is supplied in the tablet dose strengths of 20, and 40 mg.

The last approved labeling supplement, Supplement-084, was a "Changes Being Effected" supplemental new drug application that provided for the inclusion of the approved Ontario, Canada, Mylan manufacturing site name to the Mevacor package insert (PI). Additionally, this supplement includes the addition of the corporate name change. Mevacor product will be supplied from the Canada site until March 2011, and that product will expire in February 2012. This site name will be retained on the PI until all product manufacture at that site has expired. Supplement-084 was approved on February 2, 2011.

This "Prior Approval" supplemental new drug application, S-085, provides for revisions to the **CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION** sections of the Mevacor (lovastatin) package insert.

Review:

A track change version including all labeling changes since the last approved label and a final, clean version of the PI have been attached to the approval letter.

The proposed labeling changes for the Package Insert (PI) submitted February 23, 2012, PI identifier # 9844662 was deemed acceptable by Dr. Egan. A Patient Package Insert for Mevacor has never been submitted to the Agency for review. The Agency will issue an approval action on this supplement.

Reviewed by: M. A. Simoneau, R.Ph., Regulatory Project Manager/DMEP
(*See appended electronic signature page*)

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/s/

MARGARET A SIMONEAU
02/24/2012