CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-636

Generic Name: Lovastatin Tablets USP, 10 mg, 20 mg, And 40 mg

Sponsor: Eon Labs Manufacturing, Inc.

Approval Date: December 17, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
75-636

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-636

APPROVAL LETTER

ANDA 75-636

APPEARS THIS WAY ON ORIGINAL

DEC 17 2001

Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 North Conduit Avenue
Laurelton, NY 11413

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated May 14, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Lovastatin Tablets USP, 10 mg, 20 mg and 40 mg.

Reference is also made to our tentative approval letter dated July 18, 2001, and to your amendments dated July 12, 1999; September 26, October 22, and November 19, 2001.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Lovastatin Tablets USP, 10 mg, 20 mg and 40 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Mevacor® Tablets, 10 mg, 20 mg and 40 mg, respectively, of Merck Research Laboratories). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Gary Buehler 12/17/01
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-636

TENTATIVE APPROVAL LETTER

ANDA 75-636

APR 28 2000

APPEARS THIS WAY
ON ORIGINAL

Eon Labs Manufacturing, Inc.
Attention: Patricia Kaufold
227-15 North Conduit Avenue
Laurelton, NY 11413

Dear Madam:

This is in reference to your abbreviated new drug application dated May 14, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Lovastatin Tablets USP, 10 mg, 20 mg and 40 mg.

Reference is also made to your amendments dated July 12, 1999; and January 20, and March 7, 2000.

We have completed the review of this abbreviated application and have concluded that based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved.** This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug product), and is subject to change on the basis of new information that may come to our attention.

The reference listed drug product (RLD) upon which you have based your application, Mevacor Tablets of Merck Research Laboratories, is subject to a period of patent protection (U.S. Patent No. 4,231,938) which currently expires on June 15, 2001. Your application contains a Paragraph III Certification to this patent under Section 505(j)(2)(A)(vii)(III) of the Act stating that you will not market the drug product prior to the expiration of the '938 patent. Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until the period has expired, i.e., currently June 15, 2001.

Because the Agency is granting a tentative approval for this application, please submit an amendment at least 60 days (but not more than 90 days) prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as labeling, chemistry, manufacturing, and controls data as appropriate. An amendment should be submitted even if none of these changes were made. This submission should be designated clearly in your cover letter as a MINOR AMENDMENT. In addition to this amendment, the Agency may request at any time prior to the final date of approval that you submit an additional amendment containing the information described above.

Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made.

Please note that this drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book"), published by the Agency. Should you believe that there are grounds for issuing the final approval letter prior to June 15, 2001, you should amend your application accordingly.

At the time you submit any amendments, you should contact Michelle Dillahunt, Project Manager, at (301) 827-5848, for further instructions.

Sincerely yours,

/s/

Gary Buehler 4/28/00
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-636

APPROVED FINAL LABELING

Lovastatin Tablets, USP Rx only

Rev. 11/01

0000

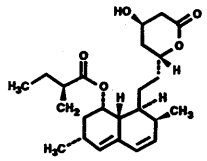
Lovastatin Tablets, USP Rx only

Lovastatin Tablets, USP
Rx only

DESCRIPTION

Lovastatin is a cholesterol lowering agent isolated from a strain of *Aspergillus terreus*. After oral ingestion, lovastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is a principal metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate limiting step in the biosynthesis of cholesterol.

Lovastatin is [1S-[1α(R*),3α,7β,8β(2S*,4S*), 8aβ]]-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate. The empirical formula of lovastatin is $C_{24}H_{36}O_5$ 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.

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

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.

Lovastatin 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 lovastatin 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 lovastatin. Since each LDL particle contains one molecule of apolipoprotein B, and since little apolipoprotein B is found in other lipoproteins, this strongly suggests that lovastatin does not merely cause cholesterol to be lost from LDL, but also reduces the concentration of circulating LDL particles. In addition, lovastatin can produce increases of variable magnitude in HDL-C, and modestly reduces VLDL-C and plasma triglycerides (TG) (see Tables I-III under *Clinical Studies*). The effects of lovastatin on Lp(a), fibrinogen, and certain other independent biochemical risk markers for coronary heart disease are unknown.

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

Pharmacokinetics

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

Following an oral dose of ^{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 lovastatin 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*).

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.

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

Clinical Studies

Lovastatin 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, lovastatin, administered in doses ranging from 10 mg q.p.m. to 40 mg b.i.d., was compared to placebo. Lovastatin consistently and significantly decreased plasma total-C, LDL-C, total-C/HDL-C ratio and LDL-C/HDL-C ratio. In addition, lovastatin produced increases of variable magnitude in HDL-C, and modestly decreased VLDL-C and plasma TG (see Tables I through III for dose response results).

The results of a study in patients with primary hypercholesterolemia are presented in Table 1.

TABLE I

Lovastatin 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
Lovastatin							
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

Lovastatin 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

Lovastatin 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)
LOVASTATIN								
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

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

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study

Lovastatin was compared to placebo in 8,245 patients with hypercholesterolemia (total-C 240-300 mg/dL [6.2mmol/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) in lovastatin treated patients were dose-related and significantly different from placebo (p≤0.001). These results were sustained throughout the study.

TABLE III

Lovastatin 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
LOVASTATIN							
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

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.

INDICATIONS AND USAGE

Therapy with lovastatin should be a component of multiple risk factor intervention in those individuals with dyslipidemia at risk for atherosclerotic vascular disease. Lovastatin 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.

Coronary Heart Disease

Lovastatin 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 artherosclerotic vascular disease due to hypercholesterolemia. Lovastatin 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.

*** Classification of Hyperlipoproteinemias

Type	Lipoproteins elevated	Lipid Elevations: major	Lipid Elevations: 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

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 x (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, lovastatin is not indicated.

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

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Placebo	33	-2	-1	-1	0	+1	+9
Lovastatin							
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

Lovastatin 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

Lovastatin 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)
LOVASTATIN								
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

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

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study

Lovastatin was compared to placebo in 8,245 patients with hypercholesterolemia (total-C 240-300 mg/dL [6.2mmol/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) in lovastatin treated patients were dose-related and significantly different from placebo (p≤0.001). These results were sustained throughout the study.

TABLE III

Lovastatin 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
LOVASTATIN							
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

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.

INDICATIONS AND USAGE

Therapy with lovastatin should be a component of multiple risk factor intervention in those individuals with dyslipidemia at risk for atherosclerotic vascular disease. Lovastatin 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.

Coronary Heart Disease

Lovastatin 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 artherosclerotic vascular disease due to hypercholesterolemia. Lovastatin 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.

*** 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

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

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

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

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

WARNINGS

Skeletal Muscle

Lovastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as muscle pain or weakness associated with grossly elevated creatine kinase (>10X the upper limit of normal [ULN]). **Rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, has been reported rarely and can occur at any time.** In the EXCEL study, 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. When drug treatment was interrupted or discontinued in these patients, muscle symptoms and creatine kinase (CK) increases promptly resolved. The risk of myopathy is increased by concomitant therapy with certain drugs, some of which were excluded by the EXCEL study design.

Myopathy caused by drug interactions.

The incidence and severity of myopathy are increased by concomitant administration of HMG-CoA reductase inhibitors with drugs that can cause myopathy when given alone, such as gemfibrozil and other fibrates, and lipid-lowering doses (≥1g/day) of niacin (nicotinic acid).

In addition, the risk of myopathy may be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Lovastatin is metabolized by the cytochrome P450 isoform 3A4 (CYP3A4). Potent inhibitors of this metabolic pathway can raise the plasma level of HMG-CoA reductase inhibitory activity and may increase the risk of myopathy. These include cyclosporine; the azole antifungals, itraconazole and ketoconazole; the macrolide antibiotics, erythromycin and clarithromycin; HIV protease inhibitors; the antidepressant nefazodone; and large quantities of grapefruit juice (> 1 quart daily) (see below; **CLINICAL PHARMACOLOGY**, *Pharmacokinetics*; **PRECAUTIONS**, *Drug Interactions;* and **DOSAGE AND ADMINISTRATION**).

Although the data are insufficient for lovastatin, the risk of myopathy appears to be increased when verapamil is used concomitantly with a closely related HMG-CoA reductase inhibitor (see **PRECAUTIONS**, *Drug Interactions*).

Reducing the risk of myopathy.

1. General measures. **Patients starting therapy with lovastatin should be advised of the risk of myopathy, and told to report promptly unexplained muscle pain, tenderness or weakness.** A creatine kinase (CK) level above 10X ULN in a patient with unexplained muscle symptoms indicates myopathy. **Lovastatin therapy should be discontinued if myopathy is diagnosed or suspected.** In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increase resolved.

Of the patients with rhabdomyolysis, many had complicated medical histories. Some had preexisting renal insufficiency, usually as a consequence of long-standing diabetes. In such patients, dose escalation requires caution. Also, as there are known adverse consequences of brief interruption of therapy, treatment with lovastatin should be stopped a few days before elective major surgery and when any major acute medical or surgical condition supervenes.

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0070

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2. **Measures to reduce the risk of myopathy caused by drug interactions (see above and PRECAUTIONS, *Drug Interactions*). Physicians contemplating combined therapy with lovastatin and any of the interacting drugs should weigh the potential benefits and risks, and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug.** Periodic CK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent myopathy.

The combined use of lovastatin with fibrates or niacin should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination. Combinations of fibrates or niacin with low doses of lovastatin have been used without myopathy in small, short-term clinical trials with careful monitoring. Addition of these drugs to lovastatin typically provides little additional reduction in LDL cholesterol, but further reductions of triglycerides and further increases in HDL cholesterol may be obtained. If one of these drugs must be used with lovastatin, clinical experience suggests that the risk of myopathy is less with niacin with the fibrates.

In patients taking concomitant cyclosporine, fibrates or niacin, the dose of lovastatin should generally not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION and DOSAGE AND ADMINISTRATION, *Concomitant Lipid-Lowering Therapy*), as the risk of myopathy increases substantially at higher doses. Concomitant use of lovastatin with itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) is not recommended. If no alternative to a short course of treatment with itraconazole, ketoconazole, erythromycin, or clarithromycin is available, a brief suspension of lovastatin therapy during such treatment can be considered as there are no known adverse consequences to brief interruptions of long-term cholesterol-lowering therapy.

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 lovastatin, symptomatic liver disease has been reported rarely at all dosages (see **ADVERSE REACTIONS**).

It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically thereafter (e.g., semiannually). Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) 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 lovastatin is recommended.

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

As with other lipid-lowering agents, moderate (less than three times the upper limit of normal) elevations of serum transaminases have been reported following therapy with lovastatin (see **ADVERSE REACTIONS**). These changes appeared soon after initiation of therapy with lovastatin, 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

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

Information for Patients

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness (see **WARNINGS**, *Skeletal Muscle*).

Drug Interactions

Gemfibrozil and other fibrates, lipid-lowering doses (≥ 1 g/day) of niacin (nicotinic acid): These drugs increase the risk of myopathy when given concomitantly with lovastatin, probably because they can produce myopathy when given alone (see **WARNINGS**, *Skeletal Muscle*). There is no evidence to suggest that these agents affect the pharmacokinetics of lovastatin.

CYP3A4 Interactions: Lovastatin has no CYP3A4 inhibitory activity; therefore, it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. However, lovastatin itself is a substrate for CYP3A4. Potent inhibitors of CYP3A4 may increase the risk of myopathy by increasing the plasma concentration of HMG-CoA reductase inhibitory activity during lovastatin therapy. These inhibitors include cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, and large quantities of grapefruit juice (>1 quart daily) (see **CLINICAL PHARMACOLOGY**, *Pharmacokinetics* and **WARNINGS**, *Skeletal Muscle*).

Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma concentrations of drugs metabolized by CYP3A4. Large quantities of grapefruit juice (>1 quart daily) significantly increase the serum concentrations of lovastatin and its β-hydroxyacid metabolite during lovastatin therapy and should be avoided (see **CLINICAL PHARMACOLOGY**, *Pharmacokinetics* and **WARNINGS**, *Skeletal Muscle*).

Although the data are insufficient for lovastatin, the risk of myopathy appears to be increased when verapamil is used concomitantly with a closely related HMG-CoA reductase inhibitor (see **WARNINGS**, *Skeletal Muscle*).

Coumarin Anticoagulants: In a small clinical trial in which lovastatin was administered to warfarin treated patients, no effect on prothrombin time was detected. However, another HMG-CoA reductase inhibitor has been found to produce a less than two-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.

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 lovastatin in hypercholesterolemic non-insulin dependent diabetic patients, there was no drug interaction with glipizide or with chlorpropamide (see **CLINICAL PHARMACOLOGY**, *Clinical Studies*).

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. However, clinical studies have shown that lovastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve, and does not reduce basal plasma testosterone concentration. Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG. In the same 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 4chromatolysis 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 lovastatin.)

There was an increase in incidence of papilloma in the nonglandular 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 at plasma levels 40 times the human exposure (for mouse fetus) and 80 times the human exposure (for rat fetus) based on mg/m^2 surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in either species at multiples of 8 times (rat) or 4 times (mouse) based on surface area. No evidence of malformations was noted in rabbits at exposures up to 3 times the human exposure (dose of 15 mg/kg/day, highest tolerated dose).

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review† of approximately 100 prospectively followed pregnancies in women exposed to lovastatin or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3 to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with lovastatin during pregnancy (see **CONTRAINDICATIONS**), treatment should be immediately discontinued as soon as pregnancy is recognized. Lovastatin 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.

†Manson, J.M., Freyssinges, C. Duoraoq, 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 lovastatin should not nurse their infants (see **CONTRAINDICATIONS**).

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Because pediatric patients are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of pediatric patients with lovastatin is not recommended at this time.

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 clinical studies conducted with lovastatin, 21% 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

Lovastatin 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 lovastatin, 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**, *Skeletal Muscle*).

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study

Lovastatin 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) %	Lovastatin 20 mg q.p.m. (N=1642) %	Lovastatin 40 mg q.p.m. (N=1645) %	Lovastatin 20 mg b.i.d. (N=1646) %	Lovastatin 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, *System/ senses:* In the E patients t experienc related to *Concom* In contro with cho were obs previousl administe Prelimina is not ass alone. In myopath niacin (ni The follo listed bel *Skeletal:* *Neurolog* impairme memory disturban *Hypersen* reported anaphyla rheumatic hemolytic urticaria, epidermal *Gastroint* cholestati necrosis, *Skin:* alop dryness o *Reproduc* *Eye:* prog *Laborato* γ-glutamyl **OVERDOS** After oral was > 15 Five health dose with overdosag patients re Until furth lovastatin The dialyz **DOSAGE A** The patier receiving lovastatin Lovastatin The usual meal. The doses; the individual Guidelines LDL-C of should be considered at intervals In patients *Skeletal M* exceed 20 Cholesterol given to re below the *Concomita* Lovastatin sequestran However, lovastatin *Muscle* and *Dosage in* In patients dosage incr necessary. **WARNINGS** **HOW SUPP** Lovastatin Lovastatin Lovastatin Lovastatin They are av *Storage* Store betwe and stored

Lovastatin Tablets, USP Rx only

Rev. 11/01

0070

Lovastatin Tablets, USP Rx only

EC 17 2001

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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.

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 lovastatin in hypercholesterolemic non-insulin dependent diabetic patients, there was no drug interaction with glipizide or with chlorpropamide (see **CLINICAL PHARMACOLOGY**, *Clinical Studies*).

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. However, clinical studies have shown that lovastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve, and does not reduce basal plasma testosterone concentration. Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG. In the same 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 lovastatin.)

There was an increase in incidence of papilloma in the nonglandular 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 at plasma levels 40 times the human exposure (for mouse fetus) and 80 times the human exposure (for rat fetus) based on mg/m^2 surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in either species at multiples of 8 times (rat) or 4 times (mouse) based on surface area. No evidence of malformations was noted in rabbits at exposures up to 3 times the human exposure (dose of 15 mg/kg/day, highest tolerated dose).

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review† of approximately 100 prospectively followed pregnancies in women exposed to lovastatin or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3 to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with lovastatin during pregnancy (see **CONTRAINDICATIONS**), treatment should be immediately discontinued as soon as pregnancy is recognized. Lovastatin 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.

†Manson, J.M., Freyssinges, C. Duoraoq, 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 lovastatin should not nurse their infants (see **CONTRAINDICATIONS**).

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Because pediatric patients are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of pediatric patients with lovastatin is not recommended at this time.

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 clinical studies conducted with lovastatin, 21% 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

Lovastatin 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 lovastatin, 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**, *Skeletal Muscle*).

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study

Lovastatin 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) %	Lovastatin 20 mg q.p.m. (N=1642) %	Lovastatin 40 mg q.p.m. (N=1645) %	Lovastatin 20 mg b.i.d. (N=1646) %	Lovastatin 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 lovastatin. The value for the placebo group was 2.5%.

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) (see **WARNINGS**, *Skeletal Muscle*).

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

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

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.

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.

OVERDOSAGE

After oral administration of lovastatin 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 lovastatin 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 lovastatin and should continue on this diet during treatment with lovastatin (see NCEP Treatment Guidelines for details on dietary therapy). Lovastatin should be given with meals.

The usual recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 10-80 mg/day in single or two divided doses; the maximum recommended dose is 80 mg/day. Doses should be individualized according to the recommended goal of therapy (see NCEP Guidelines and **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 lovastatin. A starting dose of 10 mg may be considered for patients requiring smaller reductions. Adjustments should be made at intervals of 4 weeks or more.

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

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

Concomitant Lipid-Lowering Therapy

Lovastatin is effective alone or when used concomitantly with bile-acid sequestrants. Use of lovastatin with fibrates or niacin should generally be avoided. However, if lovastatin is used in combination with fibrates and niacin, the dose of lovastatin should generally not exceed 20 mg/day (see **WARNINGS**, *Skeletal Muscle* 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**, *Skeletal Muscle*).

HOW SUPPLIED

Lovastatin Tablets, USP are Supplied as:

Lovastatin Tablets, USP 10 mg are peach, round, tablets imprinted Ɛ70

Lovastatin Tablets, USP 20 mg are light blue, round, tablets imprinted Ɛ72

Lovastatin Tablets, USP 40 mg are green, round, tablets imprinted Ɛ74

They are available in bottles of 60, 90, 500 and 1000.

Storage

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

Manufactured by
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

Rev. 11/01
MF0070REV1101
OS7694
MG #16642

FINAL PRINTED LABELS

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F). **Store in a dry place. Keep tightly closed. Protect from light.**

Dispense contents in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Issued 11/99
L6439

NDC 0185-0074-60

Lovastatin Tablets, USP

40 mg

Rx only

JUN 15 2001

60 Tablets

Eon Labs

Each tablet contains:
Lovastatin, USP 40 mg

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

APPROVED

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0074-60 0

DEC 17 2001

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F). **Store in a dry place. Keep tightly closed. Protect from light.**

Dispense contents in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Issued 11/99
L6425

NDC 0185-0074-09

Lovastatin Tablets, USP

40 mg

Rx only JUN 15 2001

90 Tablets

Eon Labs

Each tablet contains:
Lovastatin, USP 40 mg

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

APPROVED

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0074-09 8

DEC 17 2001

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F). **Store in a dry place. Keep tightly closed. Protect from light.**

Dispense contents in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Issued 11/99
L6418

NDC 0185-0074-05

Lovastatin Tablets, USP

40 mg

Rx only JUN 15 2001

500 Tablets

Eon Labs

Each tablet contains:
Lovastatin, USP 40 mg

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

APPROVED

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0074-05 1

DEC 17 2001

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F). **Store in a dry place. Keep tightly closed. Protect from light.**

Dispense contents in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Issued 11/99
L6432

NDC 0185-0074-10

Lovastatin Tablets, USP

40 mg

Rx only JUN 15 2001

1000 Tablets

Eon Labs

Each tablet contains:
Lovastatin, USP 40 mg

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

APPROVED

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0074-10 5

75-636

AP 12/17/01

FINAL PRINTED LABELS

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F). **Store in a dry place. Keep tightly closed. Protect from light.**

Dispense contents in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Issued 11/99
L6383

NDC 0185-0070-60

Lovastatin Tablets, USP

10 mg

Rx only

APPROVED

60 Tablets

Eon Labs

Each tablet contains:
Lovastatin, USP 10 mg

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

JUN 15 2001

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

DEC 17 2001

N 3 0185-0070-60 2

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F). **Store in a dry place. Keep tightly closed. Protect from light.**

Dispense contents in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Issued 11/99
L6369

NDC 0185-0070-09

Lovastatin Tablets, USP

10 mg

Rx only

APPROVED

90 Tablets

Eon Labs

Each tablet contains:
Lovastatin, USP 10 mg

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

JUN 15 2001

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

DEC 17 2001

N 3 0185-0070-09 1

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F). **Store in a dry place. Keep tightly closed. Protect from light.**

Dispense contents in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Issued 11/99
L6362

NDC 0185-0070-05

Lovastatin Tablets, USP

10 mg

Rx only

APPROVED

500 Tablets

Eon Labs

Each tablet contains:
Lovastatin, USP 10 mg

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

JUN 15 2001

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

DEC 17 2001

N 3 0185-0070-05 3

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F). **Store in a dry place. Keep tightly closed. Protect from light.**

Dispense contents in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Issued 11/99
L6376

NDC 0185-0070-10

Lovastatin Tablets, USP

10 mg

Rx only

APPROVED

1000 Tablets

Eon Labs

Each tablet contains:
Lovastatin, USP 10 mg

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

JUN 15 2001

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

DEC 17 2001

N 3 0185-0070-10 7

FINAL PRINTED LABELS

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F). **Store in a dry place. Keep tightly closed. Protect from light.**

Dispense contents in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Issued 11/99
L6411

NDC 0185-0072-60

Lovastatin Tablets, USP

20 mg

Rx only JUN 15 2001

60 Tablets

Eon Labs

Each tablet contains:
Lovastatin, USP 20 mg

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

APPROVED

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

DEC 17 2001

N 3 0185-0072-60 6

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F). **Store in a dry place. Keep tightly closed. Protect from light.**

Dispense contents in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Issued 11/99
L6397

NDC 0185-0072-09

Lovastatin Tablets, USP

20 mg

Rx only JUN 15 2001

90 Tablets

Eon Labs

Each tablet contains:
Lovastatin, USP 20 mg

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

APPROVED

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

DEC 17 2001

N 3 0185-0072-09 5

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F). **Store in a dry place. Keep tightly closed. Protect from light.**

Dispense contents in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Issued 11/99
L6390

NDC 0185-0072-05

Lovastatin Tablets, USP

20 mg

Rx only JUN 15 2001

500 Tablets

Eon Labs

Each tablet contains:
Lovastatin, USP 20 mg

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

APPROVED

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

DEC 17 2001

N 3 0185-0072-05 7

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F). **Store in a dry place. Keep tightly closed. Protect from light.**

Dispense contents in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Issued 11/99
L6404

NDC 0185-0072-10

Lovastatin Tablets, USP

20 mg

Rx only JUN 15 2001

1000 Tablets

Eon Labs

Each tablet contains:
Lovastatin, USP 20 mg

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

APPROVED

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

DEC 17 2001

N 3 0185-0072-10 1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-636

CHEMISTRY REVIEW(S)

Eon9901.004

1. CHEMISTRY REVIEW NO. 1. ANDA # **75636**

3. NAME AND ADDRESS OF APPLICANT
Eon Labs Manufacturing, Inc
227-15 N. Conduit Ave
Laurelton, NY 11413

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: MEVACOR®
Innovator Company: MERCK AND COMPANY, INC.
Patent Expiration Date: 06/15/01

Eon clarified on page 0003 that the company does not intend to market or distribute the product until after the patent expires.

The indications the proposed drug product is going to be used, active ingredient, route of administration , dosage form, strength and labeling is same as listed drug product.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used.

7. NONPROPRIETARY NAME
LOVASTATIN TABLETS USP, 10 MG, 20 MG, 40 MG

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Submission date	Submission type
05/14/99	**Original**

10. PHARMACOLOGICAL CATEGORY
CHOLESTEROL LOWERING AGENT

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

APPEARS THIS WAY
ON ORIGINAL

DMF number	DMF type	DMF holder	LOA(s)

13. DOSAGE FORM
Tablet

14. POTENCY

Strength	Strength units
10	Mg
20	Mg
40	Mg

15. CHEMICAL NAME AND STRUCTURE

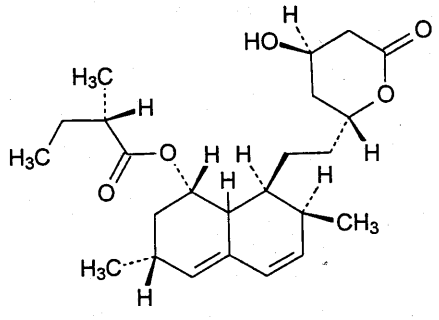
CHEMICAL NAME: Butanoic acid, 2-methyl, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl-]-1-naphthalenyl ester, [1S-[1α (R*), 3α, 7ß,8ß (2S*,4S*8),8 aß]]

CAS NUMBER: [75330-75-5]

MOLECULAR WEIGHT: 404.55

CHEMICAL FORMULA: $C_{24}H_{36}O_5$

STRUCTURE:



APPEARS THIS WAY
ON ORIGINAL

16. RECORDS AND REPORTS
N/A

17. COMMENTS
GENERAL COMMENTS:

1 Components and composition statements is acceptable.
Composition for all the strength tablets are ratio proportionate.
2. Adequate information is provided regarding facilities used for manufacturing/packaging/testing of the drug product.
3. Adequate information is submitted for manufacturing of the drug products.
4. Eon's intended production size batch is and
5. Eon has submitted adequate information for method validation for all their method for active raw material, finished drug product.
6. Eon's exhibit batches are 980616 , 980615 and 980611 and their size is tablets for all strengths.
7. Eon packaged the entire exhibit batches.
8. Eon manufactured all strength tablets without scoring just like the Listed drug product - Mevacor.
9. Release and stability specifications approved in first approved ANDA 75-451 are considered during review of this ANDA.

B: COMMENTS TO BE INCLUDED IN NA LETTER:
All the comments identified in section nos. 23, 26, 28, 29, 32, and 33, and 34 of this review.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approved. A NA letter with FAX amendment is being sent to the firm including all the deficiencies listed in this review.

19. REVIEWER:
Mujahid L. Shaikh

DATE COMPLETED:
10-25-99
Revised on 11-2-99
Revised on 11-8-99

APPEARS THIS WAY
ON ORIGINAL

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1. CHEMISTRY REVIEW NO. 2.

2. ANDA # **75636**

3. NAME AND ADDRESS OF APPLICANT
Eon Labs Manufacturing, Inc
227-15 N. Conduit Ave
Laurelton, NY 11413

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: MEVACOR®
Innovator Company: MERCK AND COMPANY, INC.
Patent Expiration Date: 06/15/01

Eon clarified on page 0003 that the company does not intend to market or distribute the product until after the patent expires.

The indications the proposed drug product is going to be used, active ingredient, route of administration , dosage form, strength and labeling is same as listed drug product.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used.

7. NONPROPRIETARY NAME
LOVASTATIN TABLETS USP, 10 MG, 20 MG, 40 MG

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Original submission: 5-14-99
* Fax Amendment: 12-7-99 (Response to 11-12-99 NA letter)

10. PHARMACOLOGICAL CATEGORY
CHOLESTEROL LOWERING AGENT

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

[redacted]

13. DOSAGE FORM
Tablet

14. POTENCY
10 mg, 20 mg and 40 mg

15. CHEMICAL NAME AND STRUCTURE

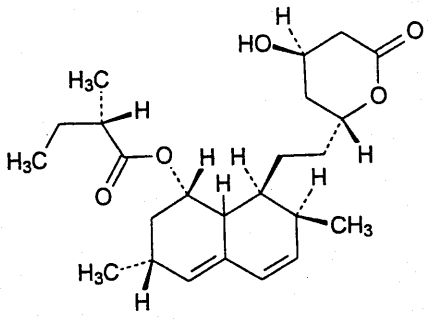
CHEMICAL NAME: Butanoic acid, 2-methyl, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl-]-1-naphthalenyl ester, [1S-[1α (R*), 3α, 7ß,8ß (2S*,4S*8),8 aß]]

CAS NUMBER: [75330-75-5]

MOLECULAR WEIGHT: 404.55

CHEMICAL FORMULA: $C_{24}H_{36}O_5$

STRUCTURE:



APPEARS THIS WAY
ON ORIGINAL

16. RECORDS AND REPORTS
N/A

17. COMMENTS
GENERAL COMMENTS:
Release and stability specifications approved in first tentatively approved ANDA 75-451 are considered during review of this ANDA. Based on this, deficiency letter is being issued.

B: COMMENTS TO BE INCLUDED IN NA LETTER:
All the comments identified in section nos. 28, 29, and 33 of this review.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approved. A NA letter with Minor amendment is being sent to the firm including all the deficiencies listed in this review.

19. REVIEWER:
Mujahid L. Shaikh

DATE COMPLETED:
12-20-99

1

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1. CHEMISTRY REVIEW NO. 3.

2. ANDA # 75-636

3. NAME AND ADDRESS OF APPLICANT
Eon Labs Manufacturing, Inc
227-15 N. Conduit Ave
Laurelton, NY 11413

APPEARS THIS WAY
ON ORIGINAL

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: MEVACOR®
Innovator Company: MERCK AND COMPANY, INC.
Patent Expiration Date: 06/15/01

Eon clarified that they do not intend to market or distribute the product until after the patent expires.

The indications the proposed drug product is going to be used, active ingredient, route of administration , dosage form, strength and labeling is same as listed drug product.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used.

7. NONPROPRIETARY NAME
LOVASTATIN TABLETS USP, 10 MG, 20 MG, 40 MG

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Original submission: 5-14-99
Fax Amendment: 12-7-99 (Response to 11-12-99 NA letter)
* Minor amendment: 1-20-00 (Response to 12-22-99 NA letter)
* Telephone amendment: 3-7-00

APPEARS THIS WAY
ON ORIGINAL

FDA:
NA letter: 11-12-99
NA letter: 12-22-99

10. PHARMACOLOGICAL CATEGORY
CHOLESTEROL LOWERING AGENT

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

[ ]

13. DOSAGE FORM
Tablet

14. POTENCY
10 mg, 20 mg and 40 mg

15. CHEMICAL NAME AND STRUCTURE

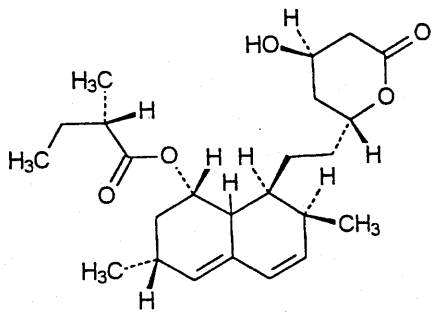
CHEMICAL NAME: Butanoic acid, 2-methyl, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl-]-1-naphthalenyl ester, [1S-[1α (R*), 3α, 7ß,8ß (2S*,4S*8),8 aß]]

CAS NUMBER: [75330-75-5]

MOLECULAR WEIGHT: 404.55

CHEMICAL FORMULA: $C_{24}H_{36}O_5$

STRUCTURE:



16. RECORDS AND REPORTS
N/A

17. COMMENTS
Referenced DMF —— is adequate per review conducted by this reviewer on 3-6-00

Release and stability specifications approved in first tentatively approved ANDA 75-451 are considered during review of this ANDA. Release and stability specifications became acceptable during this review.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved pending acceptable EER.

19. REVIEWER:
Mujahid L. Shaikh

DATE COMPLETED:
3-8-00

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1. CHEMISTRY REVIEW NO. 4.

2. ANDA # 75-636

3. NAME AND ADDRESS OF APPLICANT
Eon Labs Manufacturing, Inc
227-15 N. Conduit Ave
Laurelton, NY 11413

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: MEVACOR®
Innovator Company: MERCK AND COMPANY, INC.
Patent Expiration Date: 06/15/01

This minor amendment is submitted to get final approval for the drug product. This ANDA was tentatively approved on 4-28-00.

The indications the proposed drug product is going to be used, active ingredient, route of administration, dosage form, strength and labeling is same as listed drug product.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used.

7. NONPROPRIETARY NAME
LOVASTATIN TABLETS USP, 10 MG, 20 MG, 40 MG

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Original submission: 5-14-99
Tentative Approval: 4-28-00
Minor Amendment: 4-11-01
Telephone amendment: 5-8-01
Labeling Amendment: 6-13-01

10. PHARMACOLOGICAL CATEGORY
CHOLESTEROL LOWERING AGENT

11. Rx or OTC
Rx

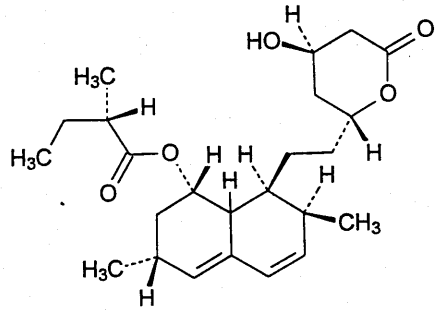
12. RELATED IND/NDA/DMF(s)

[redacted]

13. DOSAGE FORM
Tablet

14. POTENCY
10 mg, 20 mg and 40 mg

15. CHEMICAL NAME AND STRUCTURE
CHEMICAL NAME: Butanoic acid, 2-methyl, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl-]-1-naphthalenyl ester, [1S-[1□ (R*), 3□, 7ß,8ß (2S*,4S*8),8 aß]]
CAS NUMBER: [75330-75-5]
MOLECULAR WEIGHT: 404.55
CHEMICAL FORMULA: C_{24} H $_{36}O_5$
STRUCTURE:



APPEARS THIS WAY
ON ORIGINAL

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Referenced DMF [redacted] is adequate per review conducted by this reviewer on 3-6-00. This ANDA was tentatively approved based on this review of the DMF.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved.

19. REVIEWER:
Mujahid L. Shaikh

DATE COMPLETED:
5-9-01

APPEARS THIS WAY
ON ORIGINAL

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1. CHEMISTRY REVIEW NO. 5.

2. ANDA # **75-636**

3. NAME AND ADDRESS OF APPLICANT
Eon Labs Manufacturing, Inc
227-15 N. Conduit Ave
Laurelton, NY 11413

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: MEVACOR®
Innovator Company: MERCK AND COMPANY, INC.
Patent Expiration Date: 06/15/01

[ ]

The indications the proposed drug product is going to be used, active ingredient, route of administration, dosage form, strength and labeling is same as listed drug product.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used.

7. NONPROPRIETARY NAME
LOVASTATIN TABLETS USP, 10 MG, 20 MG, 40 MG

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Original submission: 5-14-99
Minor Amendment: 9-26-01

FDA:
Tentative Approval: 4-28-00
Approval: 6-15-01
Approval stayed: 6-18-01
Denial of Exclusivity remanded back to Agency: 7-3-01
Tentative Approval: 7-18-01

10. PHARMACOLOGICAL CATEGORY
CHOLESTEROL LOWERING AGENT

11. Rx or OTC
Rx

APPEARS THIS WAY
ON ORIGINAL

12. RELATED IND/NDA/DMF(s)

DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. DOSAGE FORM
Tablet

14. POTENCY
10 mg, 20 mg and 40 mg

15. CHEMICAL NAME AND STRUCTURE

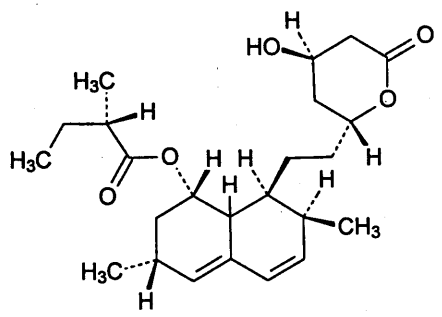
CHEMICAL NAME: Butanoic acid, 2-methyl, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl-]-1-naphthalenyl ester, [1S-[1□ (R*), 3□, 7ß,8ß (2S*,4S*8),8 aß]]

CAS NUMBER: [75330-75-5]

MOLECULAR WEIGHT: 404.55

CHEMICAL FORMULA: C_{24} H $_{36}O_5$

STRUCTURE:



16. RECORDS AND REPORTS
N/A

17. COMMENTS

APPEARS THIS WAY
ON ORIGINAL

Referenced DMF ——— is adequate per review conducted by this reviewer on 3-6-00. This ANDA was tentatively approved based on this review of the DMF.

Release and stability specifications remains acceptable during this review as no revisions are reported.

This minor amendment is submitted to get full approval of the ANDA.

No CMC changes are reported since last action.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved (Full or Tentative as OGD decides at this time).

19. REVIEWER:
Mujahid L. Shaikh

DATE COMPLETED:
10-9-01

cc: ANDA 75-636
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD- 625 /M.Shaikh/10/10/01
HFD- 625 /Mike Smela/10/11/01

V:\firmsam\eon\ltrs&rev\75636.rv5
F/T by: gp/10/24/01

/S/ 11/27/01

/S/ 11/29/01

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ON ORIGINAL

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-636

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-636 SPONSOR : Eon Labs Manufacturing, Inc.

DRUG AND DOSAGE FORM : Lovastatin, USP Tablets

STRENGTH(S) : 10, 20 and 40 mg

TYPES OF STUDIES : [SD] [SDF] MULT [OTHER]

CLINICAL STUDY SITE(S) : ———

ANALYTICAL SITE(S) : ———

STUDY SUMMARY : In single dose fasting and fed bioequivalence studies, Lovastatin, USP, 40 mg tablets were shown to be bioequivalent to Mevacor® 40 mg tablets.

DISSOLUTION : Acceptable, waiver is granted for 10 and 20 mg strengths.

DSI INSPECTION STATUS

Inspection needed: YES / [NO]	Inspection status:	Inspection results:
First Generic ____ New facility ____ For cause ____ Other ____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : MAMATA S. GOKHALE, Ph.D. BRANCH : III

INITIAL : /S/ _____ DATE : 7/26/99

TEAM LEADER : BARBARA M. DAVIT, Ph.D. BRANCH : III

INITIAL : /S/ _____ DATE : 7/26/99

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm.D.

INITIAL : /S/ _____ DATE : 8/9/99

2.1

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA # 75-636 APPLICANT: Eon Labs Manufacturing Inc.
DRUG PRODUCT: Lovastatin, USP,
10, 20 and 40 mg Tablets

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing should be incorporated in your stability and quality control programs as specified in USP 23, supplement 7, page 3902.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA # 75-636
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer: M. Gokhale
HFD-658/ TL: B. Davit

V:\NEW\FIRMSAM\ESILEDER\LTRS&REV\75636SDW.599.DOC
Printed in final on 7/26/99

Endorsements: (Final with Dates)
HFD-658/ M. Gokhale /S/ /S/ 7/26/99
HFD-658/ B. Davit /S/ 7/26/99
HFD-650/ D. Conner /S/ 8/11/99
HFD-617/ P. Nguyen /S/ 8/13/99

Bioequivalency- Acceptable Submission Date: 14 May, 1999

1) Fasting Study (STF) Strength: 40 mg
Clinical:
Analytical:
Outcome: AC

all OK
/S/ 7/26/99

2) Food Study (STP) Strength: 40 mg
Clinical:
Analytical:
Outcome: AC

3) Dissolution Waiver (DIW) Strengths: 10 and 20 mg
Outcome: AC

3) Study Amendment Strengths: 10, 20 and 40 mg
July 12, 1999 Outcome: AC

Outcome Decisions: AC- Acceptable

Winbio comments: STF - Acceptable
STP – Acceptable
DIS – Acceptable
DIW – Acceptable

Lovastatin Tablets, USP
10, 20 and 40 mg
ANDA 75-636
Reviewer: Mamata S. Gokhale
v:\new\firmsam\eon\ltrs&rev\75636sdw.599

Eon Labs Manufacturing Inc.
227-15 N. Conduit Avenue.
Laurelton NY 11413

Submission Date: May 14, 1999

Review of Bioequivalence Studies, Dissolution Data and Waiver Requests

(Electronic Submission)

Introduction

Indication: Cholesterol lowering agent
Type of Submission: Original ANDA
Contents of Submission:
40 mg Lovastatin tablets, USP: Dissolution data and in vivo bioequivalence studies measuring lovastatin (parent) and it's ß-hydroxyacid (metabolite) under fasting and fed conditions.
10 and 20 mg Lovastatin tablets, USP: Dissolution data and waiver request for in vivo bioequivalence study requirements.
RLD: Mevacor® tablets, 10, 20 and 40 mg manufactured by Merck & Co. Inc.

Background

Lovastatin, a lactone produced by fermentation of the Aspergillus terreus fungus, is indicated as an adjunct to the diet for the reduction of elevated total and LDL cholesterol levels in patients with primary hypercholesterolemia. Mevacor® is also indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease to lower total and LDL cholesterol. The starting daily dose is 40 mg taken with the evening meal and may be increased up to of 80 mg in single or two divided doses[1].

Lovastatin undergoes extensive first pass extraction in the liver[1]. Therefore, the availability of lovastatin to the general circulation is prone to pronounced inter- and intra-subject variability[1, 4] Inactive in the parent form, lovastatin is rapidly metabolised to its active ß-hydroxyacid (mevinolinic acid) and other (active) metabolites after oral administration. The hypolipemic activity of the metabolites is due to inhibition of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, which catalyzes the rate-limiting step in cholesterol synthesis. Using a specific analytical method to measure plasma concentrations of lovastatin and ß-hydroxylovastatin, it was shown that under fasting conditions, plasma concentrations of lovastatin metabolites were two thirds of those measured when the dose was given after a standard meal[1]. Based on the data on file at _____ following plasma pharmacokinetic parameters can be expected for after a single dose oral administration of 80 mg of lovastatin in healthy adult males:

Study Condition:	fasting	fasting
Length of Fasting:	10 hrs	10 hrs

Randomization		Design	
Randomized:	Y	Design Type:	crossover
No. of sequences:	2	Replicated Treatment Design:	N
No. of periods:	2	Balanced:	Y
No. of treatments:	2	Washout Period:	2 weeks

Randomization Scheme:
AB: 1,2,6,7,10,12,13,14,18,19,20,21,22,25,29,32,34,36,39,41,42,47,48,50,53,55,56,57,58,59,61
BA: 3,4,5,8,9,11,15,16,17,23,24,2627,28,30,31,33,35,37,38,40,43,44,45,46,49,51,52,54,60,62

Dosing		Subjects	
Single or multiple dose:	Single	IRB approval:	Y
Steady state:	N	Informed consent obtained:	Y
Volume of liquid intake:	240 ml	No. of subjects enrolled:	62
Route of administration:	Oral	No. of subjects completing:	60
Dosing interval:	Hr	No. of subjects plasma analyzed:	60
Number of doses:	N/A	No. of dropouts:	2
Loading dose:	mg	Sex(es) included:	male
Steady state dose time:	N/A	Healthy volunteers only:	Y
Length of infusion:	N/A	Explain if patients are enrolled:	N/A
		No. of adverse reactions/events:	28

Dietary Restrictions: No alcohol-, grapefruit- or xanthine-containing beverages and foods for the 24 hours before dosing and throughout the period of sample collection. Water intake was prohibited from one hour pre-dose until one hour post-dose.
Drug Restrictions: No medication (including over-the-counter products) for the 7 days preceding the study.
Activity Restrictions: Subjects remained ambulatory or seated upright during the first four hours following drug administration in each period (except when warranted by medical events). No strenuous activity was permitted at any time during the housing period.
Blood Sampling: Before dosing (time 0) and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60 and 72 hours post-dose.

Study Results

1) Clinical

Adverse Events:

Pre-dose: Subject #35 had runny nose but was found to be eligible by the medical officer.

Post-dose: Ten subjects experienced 28 adverse events out of which 11 events were drug related, and were resolved without medical intervention (details in vol. 1.2, Table C3, pg.2344-46).

Subject #	Period	Treatment	Symptoms	Intensity	Drug Association
2	1	A	Dizziness	Mild	Possible
32	1	A	Cramps around heart	Mild	Possible
50	1	A	Headache	Mild	Probable

58	1	A	Muscle pain	Mild	Possible
59	1	A	Headache	Mild	Probable
59	1	A	Nausea	Mild	Probable
59	1	A	Pressure increases in the head when standing	Mild	Remote
32	2	B	Flatulence	Mild	Probable
32	2	B	Cramps around heart	Mild	Possible
56	2	B	Headache	Mild	Probable
58	2	B	Nausea	Mild	Probable

Protocol Deviations: Minor deviations with respect to food consumption (unlikely to affect bioavailability) and blood collection.

Dropouts: Subjects #17 and 61 before period II due to personal reasons.

2) Analytical (Not to be released Under FOI)

Redacted 2

pages of

trade secret and/or

confidential

commercial

information

Parameter	Program	Calculation Method
AUCt	SAS	Trapezoidal Rule
Kel(λ)	SAS	Terminal Slope
thalf	SAS	0.693/kel
AUCi	SAS	AUCt + Ct/kel

Lovastatin:

Mean Plasma concentrations: Table 1 and Figure 1
Pharmacokinetic Parameters: Table 2
90% Confidence Intervals: Table 3
AUC_t/AUC_i ratios:

Drug	Mean	%CV	Range
Test	0.96	4.90	
Reference	0.95	6.10	

(Ratios were calculated by the reviewer)

Total Standard Deviation (SD) and and Root Mean Square Error (RMSE), Len-transformed PK data			
lnAUCt		lnCmax	
Total SD (Test)	Total SD (Reference)	Total SD (Test)	Total SD (Reference)
0.49	0.59	0.55	0.57
RMSE, Test and Reference combined			
0.266		0.331	

ß-Hydroxylovastatin

Mean Plasma concentrations: Table 4 and Figure 2
Pharmacokinetic Parameters: Table 5
90% Confidence Intervals: Table 6
AUC_t/AUC_i ratios:

Drug	Mean	%CV	Range
Test	0.93	8.70	
Reference	0.94	7.90	

(Ratios were calculated by the reviewer)

Total Standard Deviation (SD) and Root Mean Square Error (RMSE), Len-transformed PK data			
lnAUCt		lnCmax	
Total SD (Test)	Total SD (Reference)	Total SD (Test)	Total SD (Reference)
0.49	0.52	0.58	0.61
RMSE, Test and Reference combined			
0.238		0.322	

4) Statistical:

1) A total of 60 subjects completed the study. Plasma concentrations of lovastatin and ß-hydroxylovastatin were measured at 23 time points between 0 (pre-dose) to 72 h.
2) Arithmetic means, SD and geometric means were calculated for the bioavailability (PK) parameters, AUCt, AUCi and Cmax.
3) ANOVA with subject, sequence, period and treatment as factors was applied to the PK parameters for lovastatin and ß-hydroxylovastatin. The F-test was used to determine statistically significant differences (α=0.05) between test and reference products.

4) Bioequivalence of the test product to reference product was determined by two one sided t test with 90% C.I. contained within 0.8-1.25 for the bioavailability parameters AUCt, AUCi, and Cmax using ln-transformed data.

Comments: (on analytical and pharmacokinetic data)

1) The analytical method is acceptable.

2) The pharmacokinetic parameters and 90% confidence intervals re-calculated by the reviewer are in good agreement with the values determined by the firm.

3) During lovastatin analysis, a statistically significant period effect was seen for the parameter lnCmax while in the case of ß-hydroxylovastatin, statistically significant period and sequence effects were seen for lnCmax.

4) The 90% confidence intervals for ln-transformed AUCT, AUCi and Cmax ratios are within acceptable limits of 80-125%.

Conclusion: The fasting single dose bioequivalence study is acceptable.

Protocol No: 981778, *In-Vivo* Food Effects Bioequivalence Study Conducted Under Fasting and Non-Fasting Conditions

Study Information

Principal Investigator: [redacted]
Clinical Facility: [redacted]
Medical Direcor: [redacted]
Scientific Director: [redacted]
Clinical Study Dates: Period I: 10/19-10/22/98, Period II: 11/02-11/05/98, Period III: 11/16-11/19/98

Analytical Facility: [redacted]
Analytical Study Dates: 10/23/98 to 12/13/98
Storage Period: Up to 55 days

Treatment Information			
Treatment ID:	A	B	C
Test or Reference:	T	T	R
Product Name:	Lovastatin, USP	Lovastatin, USP	Mevacor®
Manufacturer:	Eon Labs Manufacturing Inc.	Eon Labs Manufacturing Inc.	Merck & Co.
Batch/Lot No.:	980611	980611	E1334
Dosage Form:	tablets	tablets	tablets
Strength:	40 mg	40 mg	40 mg

Dose Administered:	80 mg	80 mg	80 mg
Study Condition:	fasting	fed	fed
Length of Fasting:	10 hr	10 hr	10 hr
Food-Drug Interval:	35 min	35 min	N/A
Standardized Breakfast:	Y	Y	N
Breakfast Specifics:	1 buttered English muffin, 1 fried egg, 1 slice American cheese, 1 slice Canadian Bacon, 1serving hash brown potatoes, 180 mL orange juice, 240 mL whole milk.	N/A	1 buttered English muffin, 1 fried egg, 1 slice American cheese, 1 slice Canadian Bacon, 1 serving hash brown potatoes, 180 mL orange juice, 240 mL whole milk.

Randomization		Design	
Randomized:	Y	Design Type:	crossover
No. of sequences:	6	Replicated Treatment Design	N
No. of periods:	3	Balanced:	Y
No. of treatments:	3	Washout Period:	2 weeks

Randomization Scheme:
ACB (period 1,2,3 respectively): 6, 7, 13
BCA (period 1,2,3 respectively): 8, 12, 17, 21
BAC (period 1,2,3 respectively): 9, 10, 18
CAB (period 1,2,3 respectively): 4, 5, 15, 20
ABC (period 1,2,3 respectively): 1, 2, 3, 19
CBA (period 1,2,3 respectively): 11, 14, 16

Dosing		Subjects	
Single or multiple dose:	Single	IRB approval:	Y
Steady state:	N	Informed consent obtained:	Y
Volume of liquid intake:	240 ml	No. of subjects enrolled:	21
Route of administration:	Oral	No. of subjects completing:	20
Dosing interval:	Hours	No. of subjects plasma analyzed:	20
Number of doses:	N/A	No. of dropouts:	1
Loading dose:	mg	Sex(es) included:	male
Steady state dose time:	N/A	Healthy volunteers only:	Y
Length of infusion:	N/A	No. of adverse events:	33

Dietary Restrictions: No alcohol-, grapefruit- or xanthine-containing beverages and foods for the 24 hours before dosing and throughout the period of sample collection. Water intake was prohibited from one hour pre-dose until one hour post-dose.
Drug Restrictions: No medication (including over-the-counter products) for the 7 days preceding the study.
Activity Restrictions: Subjects remained ambulatory or seated upright during the first four hours following drug administration in each period (except when warranted by medical events). No strenuous activity was permitted at any time during the housing period.
Blood Sampling: Before dosing (time 0) and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60 and 72 hours post-dose.

Study Results

1) Clinical

Adverse Events: Nine subjects experienced 33 adverse events out of which 22 events were drug

related and were resolved without medical intervention (details in vol. 1.20, Table C4, pg.8888-93).

Subject #	Period	Treatment	Symptoms	Intensity	Drug Association
2	1	A	Dizziness	Mild	Probable
2	1	A	Weakness	Mild	Possible
2	1	A	Dizziness	Mild	Possible
4	2	A	Headache	Mild	Possible
18	2	A	Headache	Mild	Probable
2	2	B	Dizziness	Mild	Probable
2	2	B	Headache	Mild	Possible
4	3	B	Headache	Mild	Possible
12	1	B	Burning sensation in the eyes	Mild	Remote
12	1	B	Weakness	Mild	Remote
16	2	B	Dizziness	Mild	Possible
16	2	B	Headache	Mild	Possible
16	2	B	Small papules on left forearm	Mild	Possible
16	2	B	Vomiting	Mild	Possible
16	2	B	Loose stool	Mild	Possible
21	1	B	Headache on the left	Mild	Probable
21	1	B	Pulling sensation in left eye	Mild	Probable
16	1	C	Dizziness	Mild	Remote
16	1	C	Dizziness	Moderate	Possible
16	1	C	Left arm shaking	Mild	Remote
18	3	C	Headache	Mild	Probable
21	2	C	Headache	Mild	Probable

Protocol Deviations: Minor deviations with respect to food consumption (unlikely to affect bioavailability) and blood collection.
Dropouts: Subject #1 at period II check in due to positive drug screen (urine)

2) Analytical:

[redacted]

3) Pharmacokinetic:

Parameter	Program	Calculation Method
AUCt	SAS	Trapezoidal Rule
Kel(λ)	SAS	Terminal Slope
thalf	SAS	0.693/kel
AUCi	SAS	AUCt + Ct/kel

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Lovastatin:
Mean Plasma concentrations: Table 7 and Figure 3
Pharmacokinetic Parameters: Table 8
LSM and Geometric means ratios: Table 9

AUCt/AUCi ratios:

Drug	Mean	%CV	Range
Test (fed)	0.96	3.30	
Reference (fed)	0.97	2.40	
Test (fasting)	0.95	5.30	

(Ratios were calculated by the reviewer)

ß-Hydroxylovastatin
Mean Plasma concentrations: Table 10 and Figure 4
Pharmacokinetic Parameters: Table 11
LSM and Geometric means ratios: Table 12
AUCt/AUCi ratios:

Drug	Mean	%CV	Range
Test (fed)	0.97	2.00	
Reference (fed)	0.98	1.80	
Test (fasting)	0.95	4.20	

(Ratios were calculated by the reviewer)

4) Statistical:

1) Twelve healthy, male subjects completed this three-treatment crossover study.

2) Arithmetic means, SD and geometric means were calculated for AUCt, AUCi and Cmax. PK parameters were analyzed by ANOVA and F-test was used to determine statistically significant differences (α=0.05) between test and reference products.
3) Bioequivalence of the test product to reference product was determined by LSM ratios and geometric means ratios contained within 0.8-1.25 for lnAUCt, lnAUCi and lnCmax.

Comments: (on analytical and pharmacokinetic data)

1) The pharmacokinetic parameters, re-calculated by the reviewer, are in good agreement with the values determined by the firm.

2) Under fed conditions, the test/reference LSM ratios are within the acceptable range of 0.80-1.25. The test/reference Geometric mean ratios are also within acceptable range of 0.80-1.25.

3) There were no statistically significant period or sequence effects for any of the PK parameters in the analysis of lovastatin and ß-hydroxylovastatin.

Conclusion: The single dose post prandial bioequivalence study is acceptable.

Dissolution Data and Waiver Request

The applicant is requesting a waiver of in vivo bioequivalence testing for the 20 and 10 mg dosage strengths. Comparative dissolution profiles were provided for Merck and Co's Mevacor® tablets, 10, 20 and 40 mg strengths and Eon's Lovastatin, USP, tablets, 10, 20 and 40 mg strengths. A full list of components in Eon's Lovastatin, USP, tablets was also provided for all the strengths.

Reference Product:	**10 mg Lot # E1280**	Expiration Date: 5/1999
Test Product:	**10 mg Lot # 980616**	Expiration Date: N/A
Reference Product:	**20 mg Lot # E18509**	Expiration Date: 8/99
Test Product:	**20 mg Lot # 980615**	Expiration Date: N/A
Reference Product:	**40 mg Lot # E1334**	Expiration Date: 10/1999
Test Product:	**40 mg Lot # 980611**	Expiration Date: N/A

Formulation: (Not to be released under FOI)

The composition of the **Lovastatin, USP, tablets** is as follows:

Ingredient	Amount (mg) Per Dosage Unit Strength		
	10 mg	20 mg	40 mg
[1]Lovastatin, USP	10	20	40
Lactose Monohydrate, NF			
Pregelatinized Starch NF			
Microcrystalline Cellulose, NF			
Butylated Hydroxyanisole, NF			

Magnesium Stearate, NF			
Red Iron Oxide		-	-
Yellow Iron Oxide		-	-
FD&C Blue # 2 Aluminium Lake	-		
D&C Yellow # 10 Aluminium Lake	-		
Total			

[1]Active ingredient, All inactive ingredients are within approved safety limits (FDA Inactive Ingredient Guide, Jan., 1996), All ingredients are proportionally scaled up to the batch sizes of ' tablets.

IN VITRO DISSOLUTION TESTING

Test Drug: Lovastatin, USP, Tablets, manufactured by Eon Labs Manufacturing.Inc.
Reference Drug: Mevacor® tablets manufactured by Merck & Co.
Dose Strength: 10 mg

I. Conditions for Dissolution/Release Testing:

Apparatus: USP 23 paddle at 50 rpm
Medium: Phosphate Buffer with 2% SDS, pH of 7.00, Volume: 900mL
No. Units Tested: 12
Assay Method·
Tolerance (Q): NLT (Q) in 30 minutes

II. Results of *In Vitro* Dissolution/Release Testing:

Sampling Times (min)	Test Product Lot No.: 980616			Reference Product Lot No.: E1280		
	Mean %	Range	% CV	Mean %	Range	% CV
10	90		2.80	80		3.90
20	100		0.50	94		0.80
30	100		0.50	96		0.60
45	100		0.50	98		0.60

Test Drug: Lovastatin, USP, Tablets, manufactured by Eon Labs Manufacturing.Inc.
Reference Drug: Mevacor® tablets manufactured by Merck & Co.
Dose Strength: 20 mg

I. Conditions for Dissolution/Release Testing: Same as for 10 mg strength

II. Results of *In Vitro* Dissolution/Release Testing:

Sampling Times (min)	Test Product Lot No.: 980615			Reference Product Lot No.: E18509		
	Mean %	Range	% CV	Mean %	Range	% CV
10	88		4.00	93		0.90
20	98		0.50	97		0.50
30	100		0.40	98		0.50
45	100		0.30	98		0.50

Test Drug: Lovastatin, USP, Tablets, manufactured by Eon Labs Manufacturing.Inc.
Reference Drug: Mevacor® tablets manufactured by Merck & Co.
Dose Strength: 40 mg

I. Conditions for Dissolution/Release Testing: Same as for 10 mg strength

II. Results of *In Vitro* Dissolution/Release Testing:

Sampling Times (min)	Test Product Lot No.: 980611			Reference Product Lot No.: E1334		
	Mean %	Range	% CV	Mean %	Range	% CV
10	94		1.20	87		2.10
20	100		1.00	95		1.40
30	101		0.90	97		1.30
45	101		0.90	98		1.20

f2 factor across different strengths		
Strength	**Test vs Reference**	
10 mg	64	
20 mg	80	
[1]40 mg	70	
f2 factor across test and reference products		
Product	[1]40 mg vs 10 mg	[1]40 mg vs 20 mg
Test	87	79
Reference	76	78

[1]Used in the *in vivo* studies.

Comments: (on formulation and dissolution testing)

[redacted]

2) The dissolution testing was carried out in 900 mL of phosphate buffer with 2 % SDS, pH 7.00, using USP 23 paddle apparatus at 50 RPM, as per recommendations in the Pharmacopeal Forum, Seventh Supplement, USP-NF, Nov. 15, 1997, pg. 3902.

3) The dissolution testing data for 10, 20 and 40 mg of Lovastatin, USP, tablets are comparable with the RLD at later time intervals (30 and 45 min.).

4) The Similarity factor (f2) is between 50 and 100 for all dissolution profile comparisons. This suggests that dissolution profiles of 10 and 20 mg strengths of the test product are similar to 40 mg strength used in the *in vivo* studies and all three strengths are similar to the respective reference products.

5) The test products of all strengths comfortably meet the respective dissolution specification of NLT — (Q) in 30 min.

Recommendations:

1) The fasting single dose bioequivalence study, protocol # 981777 and post prandial bioequivalence study, protocol # 981778, conducted by Eon Labs Manufacturing Inc., on its Lovastatin, USP, tablets, 40 mg, Lot # 980611, comparing it to Mevacor® 40 mg tablets manufactured by Merck & Co., Lot # E1334 have been found to be acceptable by the Division of Bioequivalence. The studies demonstrate that Eon's Lovastatin, USP, tablets, 40 mg strength, are bioequivalent to Merck's Mevacor® 40 mg tablets.

2) In vitro dissolution testing conducted by Eon Labs Manufacturing Inc., on its Lovastatin, USP, tablets, 10, 20 and 40 mg, Lot # 980616, 980615 and 980611 respectively, meets the specifications indicated below.

3) Formulations of the 10 and 20 mg strengths are proportional to that of the 40 mg strength, which underwent bioequivalence testing. Moreover, dissolution profiles of the lower 10 and 20 mg strengths are similar to the 40 mg strength. Waiver of in vivo bioequivalence testing requirements for the 10 and 20 mg strengths is granted. The Division of Bioequivalence deems Lovastatin, USP, tablets, 10, 20 and 40 mg, manufactured by Eon Labs manufacturing Inc., to be bioequivalent to Mevacor® tablets, 10, 20 and 40 mg, manufactured by Merck & Co.

4) The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. Dissolution testing should be conducted in 900 mL of phosphate buffer with 2% SDS, pH 7.00, at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than — (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

5) The firm has met the requirements of *in vivo* bioequivalence and *in vitro* dissolution testing.

6) The firm should be informed of the above recommendations.

/S/ 7/26/99

Mamata S. Gokhale, Ph.D.
Review Branch III
Division of Bioequivalence

/S/ 7/26/99

RD INITIALED BDAVIT
FT INITIALED BDAVIT /S/ Date 7/26/99

Concur: /S/ Date 8/11/99

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

cc: ANDA# 75636 (original, duplicate), Gokhale, HFD-658, Drug File, Division File

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Table 1

Mean Plasma Concentrations of Lovastatin

following an oral dose of 80 mg under fasting conditions,
Treatment A: Lovastatin, USP, 2x40 mg tablets, Lot # 980611
Treatment B: Mevacor®, 2x40 mg tablets, Lot # E1334

Time (hours)	Mean Plasma Concentrations (ng/ml) Mean , SD				
	Treatment A		Treatment B		Ratio A/B
0.00	0.00	0.00	0.00	0.00	0.00
0.25	0.02	0.06	0.04	0.09	0.50
0.50	0.25	0.31	0.35	0.36	0.71
1.00	1.11	1.06	1.31	1.32	0.85
1.50	2.07	1.92	2.38	2.57	0.87
2.00	2.86	2.51	3.25	3.06	0.88
2.50	3.50	2.86	4.15	4.24	0.84
3.00	4.03	3.25	4.70	4.02	0.86
3.50	4.59	3.63	5.01	4.35	0.92
4.00	4.55	3.39	5.20	3.84	0.88
4.50	4.77	3.19	5.58	4.00	0.85
5.00	3.58	2.17	3.97	2.58	0.90
6.00	2.80	1.62	2.90	1.74	0.97
7.00	2.68	1.50	2.68	1.53	1.00
8.00	2.69	1.47	2.70	1.60	1.00
10.00	2.74	1.45	2.82	1.93	0.97
12.00	2.69	1.67	2.67	2.09	1.01
16.00	2.53	1.72	2.41	2.30	1.05
24.00	2.26	1.49	2.11	1.63	1.07
36.00	1.28	1.15	1.25	1.26	1.02
48.00	0.56	0.56	0.48	0.51	1.17
60.00	0.24	0.32	0.26	0.44	0.92
72.00	0.12	0.21	0.15	0.25	0.80

Table 2
Lovastatin Pharmacokinetic Parameters
Single Dose Fasting Study, 80 mg Dose
Treatment A: Lovastatin, USP, 2x40 mg tablets, Lot # 980611
Treatment B: Mevacor®, 2x40 mg tablets, Lot # E1334

Plasma Parameters	Cmax (ng/ml)		Tmax (hours)		Kel (1/hours)	
Treatment	A	B	A	B	A	B
MEAN	6.20	6.59	6.72	6.18	0.08	0.08
S.D.	4.17	4.28	4.64	4.19	0.04	0.03
CV%	67.31	64.91	69.11	67.72	47.23	42.65
MIN						
MAX						

Plasma Parameters	T1/2 (hours)		AUCt (ng/ml-hours)		AUCi (ng/ml-hours)	
Treatment	A	B	A	B	A	B
MEAN	10.23	10.84	106.80	105.21	114.44	116.25
S.D.	5.44	5.74	54.09	59.07	54.68	59.33
CV%	53.13	52.94	50.64	56.15	47.78	51.04
MIN						
MAX						

Table 3
Summary Statistics for Lovastatin
Single Dose Fasting Study, 240 mg Dose
Treatment A: Lovastatin, USP, 2x40 mg tablets, Lot # 980611
Treatment B: Mevacor®, 2x40 mg tablets, Lot # E1334

PK Parameter	LS Mean		Ratio	Geometric Mean		Ratio	90% C.I.
(Treatment)	A	B	A/B	A	B	A/B	
ln AUCt (ng·hr/mL)	4.55	4.49	1.01	94.96	89.32	1.06	98-115
ln AUCi (ng·hr/mL)	4.63	4.62	1.00	98.04	99.20	0.99	91-107
lnCmax (ng·hr/mL)	1.67	1.72	0.97	5.29	5.59	0.95	85-105

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Table 4

Mean Plasma Concentrations of ß-Hydroxylovastatin

following an oral dose of 80 mg under fasting conditions,
Treatment A: Lovastatin, USP, 2x40 mg tablets, Lot # 980611
Treatment B: Mevacor®, 2x40 mg tablets, Lot # E1334

Time (hours)	Mean Plasma Concentrations (ng/ml) Mean , SD				
	Treatment A		Treatment B		Ratio A/B
0.00	0.00	0.00	0.00	0.00	0.00
0.25	0.23	0.35	0.36	0.65	0.64
0.50	1.25	1.20	1.68	1.94	0.74
1.00	3.06	4.01	3.20	2.98	0.96
1.50	3.32	3.86	3.81	3.74	0.87
2.00	3.11	3.28	3.63	2.75	0.86
2.50	2.90	2.77	3.46	3.14	0.84
3.00	2.67	2.23	3.24	2.89	0.82
3.50	2.65	2.21	2.93	2.38	0.90
4.00	2.45	1.85	2.79	2.20	0.88
4.50	3.10	2.21	3.61	2.63	0.86
5.00	4.16	2.46	4.29	2.57	0.97
6.00	4.10	2.32	4.32	2.55	0.95
7.00	3.68	2.44	3.89	2.94	0.95
8.00	3.33	2.24	3.25	2.20	1.02
10.00	3.70	2.38	3.74	2.45	0.99
12.00	3.42	2.08	3.46	2.55	0.99
16.00	2.60	1.82	2.46	1.88	1.06
24.00	2.44	1.72	2.32	1.68	1.05
36.00	1.18	0.96	1.05	0.90	1.12
48.00	0.50	0.49	0.52	0.58	0.96
60.00	0.15	0.26	0.13	0.22	1.15
72.00	0.07	0.16	0.07	0.15	1.00

Table 5
ß-Hydroxylovastatin Pharmacokinetic Parameters
Single Dose Fasting Study, 80 mg Dose
Treatment A: Lovastatin, USP, 2x40 mg tablets, Lot # 980611
Treatment B: Mevacor®, 2x40 mg tablets, Lot # E1334

Plasma Parameters	Cmax (ng/ml)		Tmax (hours)		Kel (1/hours)	
Treatment	A	B	A	B	A	B
MEAN	5.82	6.68	8.79	7.76	0.07	0.07
S.D.	3.54	4.88	7.87	6.70	0.04	0.03
CV%	60.74	72.96	89.53	86.28	51.59	44.07
MIN						
MAX						

Plasma Parameters	T1/2 (hours)		AUCt (ng/ml-hours)		AUCi (ng/ml-hours)	
Treatment	A	B	A	B	A	B
MEAN	12.00	12.74	101.42	101.37	109.33	112.51
S.D.	5.99	10.32	48.03	61.79	49.69	66.72
CV%	49.89	80.97	47.36	60.95	45.45	59.30
MIN						
MAX						

Table 6
Summary Statistics for ß-Hydroxylovastatin
Single Dose Fasting Study, 240 mg Dose
Treatment A: Lovastatin, USP, 2x40 mg tablets, Lot # 980611
Treatment B: Mevacor®, 2x40 mg tablets, Lot # E1334

PK Parameter	LS Mean		Ratio	Geometric Mean		Ratio	90% C.I.
(Treatment)	A	B	A/B	A	B	A/B	
ln AUCt (ng·hr/mL)	4.51	4.48	1.02	90.77	88.08	1.03	96-111
ln AUCi (ng·hr/mL)	4.59	4.60	1.00	100.71	94.20	1.07	97-118
lnCmax (ng·hr/mL)	1.60	1.70	0.94	4.93	5.48	0.90	82-99

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ON ORIGINAL

Table 7

Mean Plasma Concentrations of lovastatin following an oral dose of 80 mg

Treatment A: Lovastatin, USP, 2x40 mg tablets, Lot # 980611 under fasting conditions
Treatment B: Lovastatin, USP, 2x40 mg tablets, Lot # 980611 under fed conditions
Treatment C: Mevacor®, 2x40 mg tablets, Lot # E1334 under fed conditions

Time (hours)	Plasma Conc. (ng/ml), Mean, S.D.							
	Treatment A		Treatment B		Treatment C		Ratio B/A	Ratio B/C
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.25	0.12	0.23	0.32	0.43	0.73	2.08	2.67	0.44
0.50	1.34	1.90	3.75	4.54	3.27	5.55	2.80	1.15
1.00	2.87	2.94	14.08	12.42	8.01	9.34	4.91	1.76
1.50	3.19	2.91	15.98	12.54	10.89	10.57	5.01	1.47
2.00	2.96	2.27	13.79	11.42	10.88	9.03	4.66	1.27
2.50	2.97	2.54	11.06	10.32	10.14	6.88	3.72	1.09
3.00	2.52	1.74	8.60	8.19	10.13	9.79	3.41	0.85
3.50	2.58	2.04	6.50	5.71	10.78	16.78	2.52	0.60
4.00	2.38	1.76	5.08	4.68	9.07	15.08	2.13	0.56
4.50	3.48	2.39	4.33	3.97	8.82	17.79	1.24	0.49
5.00	4.54	2.54	3.30	2.76	6.60	12.79	0.73	0.50
6.00	4.52	2.58	2.26	2.24	3.90	6.82	0.50	0.58
7.00	4.31	2.57	1.71	1.69	2.96	5.07	0.40	0.58
8.00	3.78	2.61	1.45	1.47	2.21	3.66	0.38	0.66
10.00	4.34	3.18	1.18	1.25	1.55	2.36	0.27	0.76
12.00	2.90	1.66	0.83	0.91	0.97	1.33	0.29	0.86
16.00	2.36	1.72	0.51	0.66	0.62	0.93	0.22	0.82
24.00	2.27	1.94	0.37	0.42	0.51	0.88	0.16	0.73
36.00	1.16	0.96	0.12	0.19	0.14	0.25	0.10	0.86
48.00	0.55	0.53	0.05	0.11	0.04	0.11	0.09	1.25
60.00	0.15	0.18	0.00	0.00	0.01	0.02	0.00	0.00
72.00	0.06	0.10	0.00	0.00	0.00	0.00	0.00	0.00

Table 8
Lovastatin Pharmacokinetic Parameters
Single Dose Fed and Fasting Study, 80 mg Dose
Treatment A: Lovastatin, USP, 2x40 mg tablets, Lot # 980611 under fasting conditions
Treatment B: Lovastatin, USP, 2x40 mg tablets, Lot # 980611 under fed conditions
Treatment C: Mevacor®, 2x40 mg tablets, Lot # E1334 under fed conditions

Plasma Parameters	Cmax (ng/ml)			Tmax (hours)			Kel (1/hours)		
Treatment	A	B	C	A	B	C	A	B	C
MEAN	5.82	17.73	17.93	9.50	1.69	1.97	0.07	0.16	0.16
S.D.	3.12	13.82	18.13	8.41	0.82	0.92	0.04	0.13	0.10
CV%	53.64	77.98	101.07	88.51	48.69	46.40	55.38	81.90	65.55
MIN									
MAX									

Plasma Parameters	T1/2 (hours)			AUCt (ng/ml-hours)			AUCi (ng/ml-hours)		
Treatment	A	B	C	A	B	C	A	B	C
MEAN	11.74	8.24	6.66	105.07	62.61	72.13	111.62	65.01	73.83
S.D.	5.90	6.27	4.18	58.01	50.24	81.65	61.30	50.74	82.42
CV%	50.29	76.13	62.74	55.21	80.24	113.20	54.92	78.06	111.63
MIN									
MAX									

Table 9
Summary Statistics for Lovastatin
Single Dose Fed and Fasting Study, 80 mg Dose
Treatment A: Lovastatin, USP, 2x40 mg tablets, Lot # 980611 under fasting conditions
Treatment B: Lovastatin, USP, 2x40 mg tablets, Lot # 980611 under fed conditions
Treatment C: Mevacor®, 2x40 mg tablets, Lot # E1334 under fed conditions

PK Parameter	LS Mean		Ratio	Geometric Mean		Ratio
(Treatment)	B	C	B/C	B	C	B/C
ln AUCt (ng·hr/mL)	3.91	3.88	1.01	49.90	48.42	1.03
ln AUCi (ng·hr/mL)	3.96	3.91	1.01	52.46	49.90	1.05
lnCmax (ng·hr/mL)	2.58	2.58	1.00	13.20	13.20	1.00

PK Parameter	LS Mean		Ratio	Geometric Mean		Ratio
(Treatment)	B	A	B/A	B	A	B/A
ln AUCt (ng·hr/mL)	3.91	4.51	0.86	49.90	90.02	0.55
ln AUCi (ng·hr/mL)	3.96	4.57	0.86	52.46	96.54	0.54
lnCmax (ng·hr/mL)	2.58	1.61	1.58	13.20	5.00	2.63

APPEARS THIS WAY
ON ORIGINAL

Table 10

Mean Plasma Concentrations of ß-hydroxylovastatin following an oral dose of 80 mg

Treatment A: Lovastatin, USP, 2x40 mg tablets, Lot # 980611 under fasting conditions

Treatment B: Lovastatin, USP, 2x40 mg tablets, Lot # 980611 under fed conditions

Treatment C: Mevacor®, 2x40 mg tablets, Lot # E1334 under fed conditions

Time (hours)	Plasma Conc. (ng/ml), Mean, S.D.							
	Treatment A		Treatment B		Treatment C		Ratio B/A	Ratio B/C
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.25	0.02	0.05	0.01	0.04	0.05	0.18	0.50	0.20
0.50	0.26	0.23	0.26	0.34	0.28	0.75	1.00	0.93
1.00	1.05	0.76	2.26	2.07	1.25	1.77	2.15	1.81
1.50	1.86	1.14	4.46	2.90	2.84	2.42	2.40	1.57
2.00	2.54	1.45	6.59	3.21	4.69	2.86	2.59	1.41
2.50	3.34	1.70	7.96	3.76	6.68	3.67	2.38	1.19
3.00	3.83	1.87	9.03	4.52	8.54	4.53	2.36	1.06
3.50	4.09	2.00	10.02	5.21	11.53	7.47	2.45	0.87
4.00	4.14	1.92	9.97	5.21	12.71	9.58	2.41	0.78
4.50	4.62	1.80	10.35	6.16	15.47	14.17	2.24	0.67
5.00	3.31	1.21	8.5	5.55	12.24	11.87	2.57	0.69
6.00	2.71	1.12	5.73	4.07	7.47	5.62	2.11	0.77
7.00	2.80	1.38	4.19	6.02	6.06	5.08	1.50	0.69
8.00	3.15	2.27	3.71	2.55	4.97	4.56	1.18	0.75
10.00	3.81	2.34	2.62	1.82	3.38	3.47	0.69	0.78
12.00	3.78	2.54	1.85	1.54	2.21	2.26	0.49	0.84
16.00	2.34	1.41	0.77	0.79	0.90	1.04	0.33	0.86
24.00	1.83	1.44	0.34	0.45	0.48	0.83	0.19	0.71
36.00	0.90	1.05	0.12	0.27	0.15	0.35	0.13	0.80
48.00	0.74	1.33	0.07	0.13	0.08	0.23	0.09	0.88
60.00	0.36	0.65	0.02	0.07	0.02	0.06	0.06	1.00
72.00	0.14	0.34	0.01	0.03	0.01	0.04	0.07	1.00

Table 11

ß-hydroxylovastatin **Pharmacokinetic Parameters**

Single Dose Fed and Fasting Study, 80 mg Dose

Treatment A: Lovastatin, USP, 2x40 mg tablets, Lot # 980611 under fasting conditions

Treatment B: Lovastatin, USP, 2x40 mg tablets, Lot # 980611 under fed conditions

Treatment C: Mevacor®, 2x40 mg tablets, Lot # E1334 under fed conditions

Plasma Parameters	Cmax (ng/ml)			Tmax (hours)			Kel (1/hours)		
Treatment	A	B	C	A	B	C	A	B	C
MEAN	5.52	11.97	16.15	6.97	3.69	4.36	0.07	0.20	0.20
S.D.	2.25	6.18	13.95	3.72	1.02	1.19	0.04	0.12	0.10
CV%	40.75	51.59	86.38	53.35	27.52	27.19	55.34	63.43	51.32
MIN									
MAX									

Plasma Parameters	T1/2 (hours)			AUCt (ng/ml-hours)			AUCi (ng/ml-hours)		
Treatment	A	B	C	A	B	C	A	B	C
MEAN	11.96	5.69	4.94	100.55	72.21	87.96	108.59	74.26	86.91
S.D.	5.92	4.44	3.40	71.47	36.86	72.63	77.02	37.83	74.27
CV%	49.49	78.05	68.95	71.08	51.05	82.57	70.92	50.94	85.45
MIN									
MAX									

Table 12

Summary Statistics for ß-hydroxylovastatin

Single Dose Fed and Fasting Study, 80 mg Dose

Treatment A: Lovastatin, USP, 2x40 mg tablets, Lot # 980611 under fasting conditions

Treatment B: Lovastatin, USP, 2x40 mg tablets, Lot # 980611 under fed conditions

Treatment C: Mevacor®, 2x40 mg tablets, Lot # E1334 under fed conditions

PK Parameter	LS Mean		Ratio	Geometric Mean		Ratio
(Treatment)	B	C	B/C	B	C	B/C
ln AUCt (ng·hr/mL)	4.13	4.18	0.99	62.18	65.37	0.95
ln AUCi (ng·hr/mL)	4.15	4.21	0.99	63.43	67.36	0.94
lnCmax (ng·hr/mL)	2.35	2.48	0.95	10.49	11.94	0.88

PK Parameter	LS Mean		Ratio	Geometric Mean		Ratio
(Treatment)	B	A	B/A	B	A	B/A
ln AUCt (ng·hr/mL)	4.13	4.39	0.94	62.18	80.64	0.77
ln AUCi (ng·hr/mL)	4.15	4.46	0.93	63.43	86.49	0.73
lnCmax (ng·hr/mL)	2.35	1.57	1.50	10.49	4.81	2.18

Figure 1

Mean Plasma Concentrations of Lovastatin, (Lovastatin, USP, 2x40 mg Tablets) under Fasting Conditions, Test (Trt A) vs Reference (Trt B)

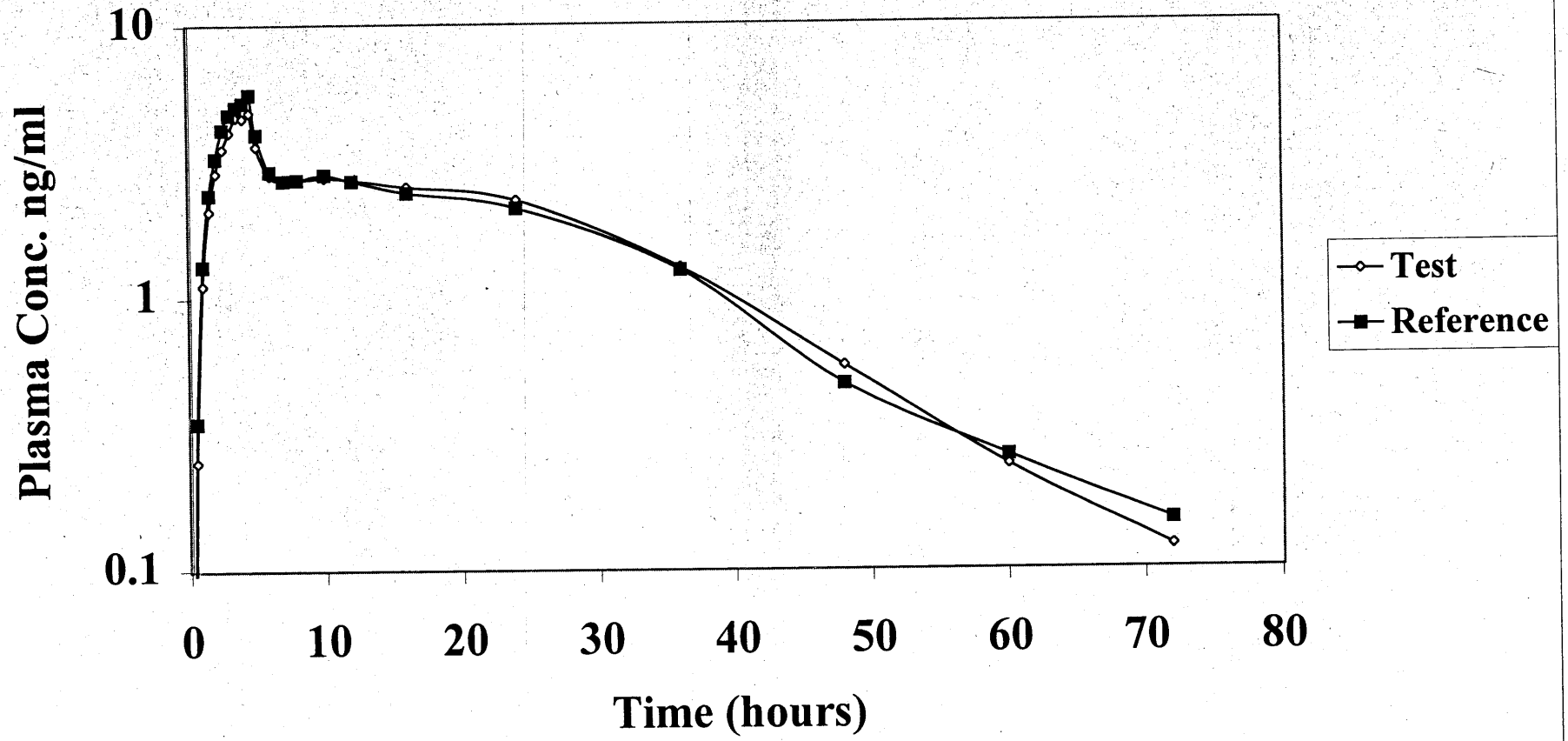


Figure 1

Mean Plasma Concentrations of Lovastatin, (Lovastatin, USP, 2x40 mg Tablets) under Fasting Conditions, Test (Trt A) vs Reference (Trt B)

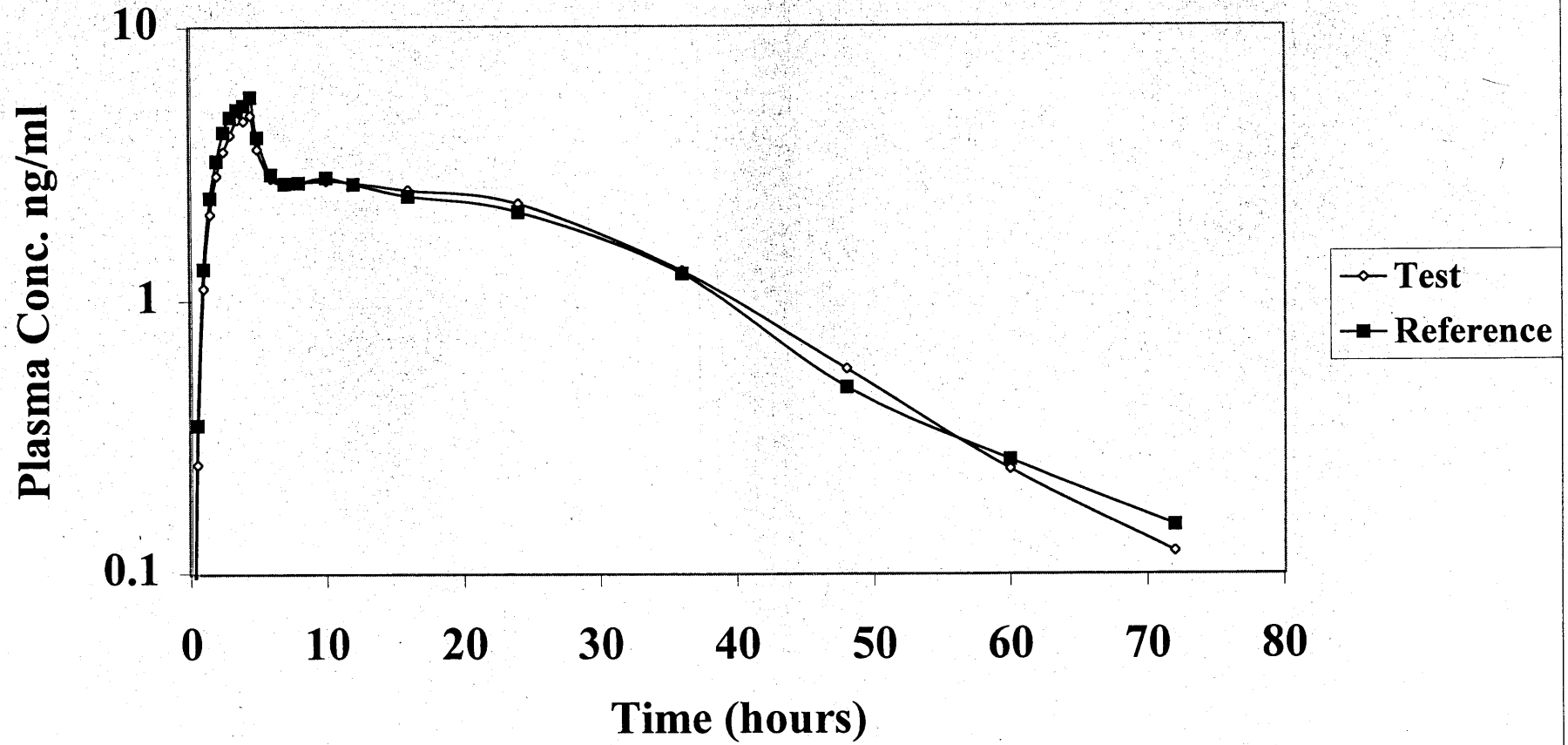


Figure 3

Plasma Concentrations of Lovastatin under Fed and Fasting Conditions after Oral Dose of 80 mg Lovastatin, USP, (Test) or Mevacor (Reference) Tablets (2x40 mg)

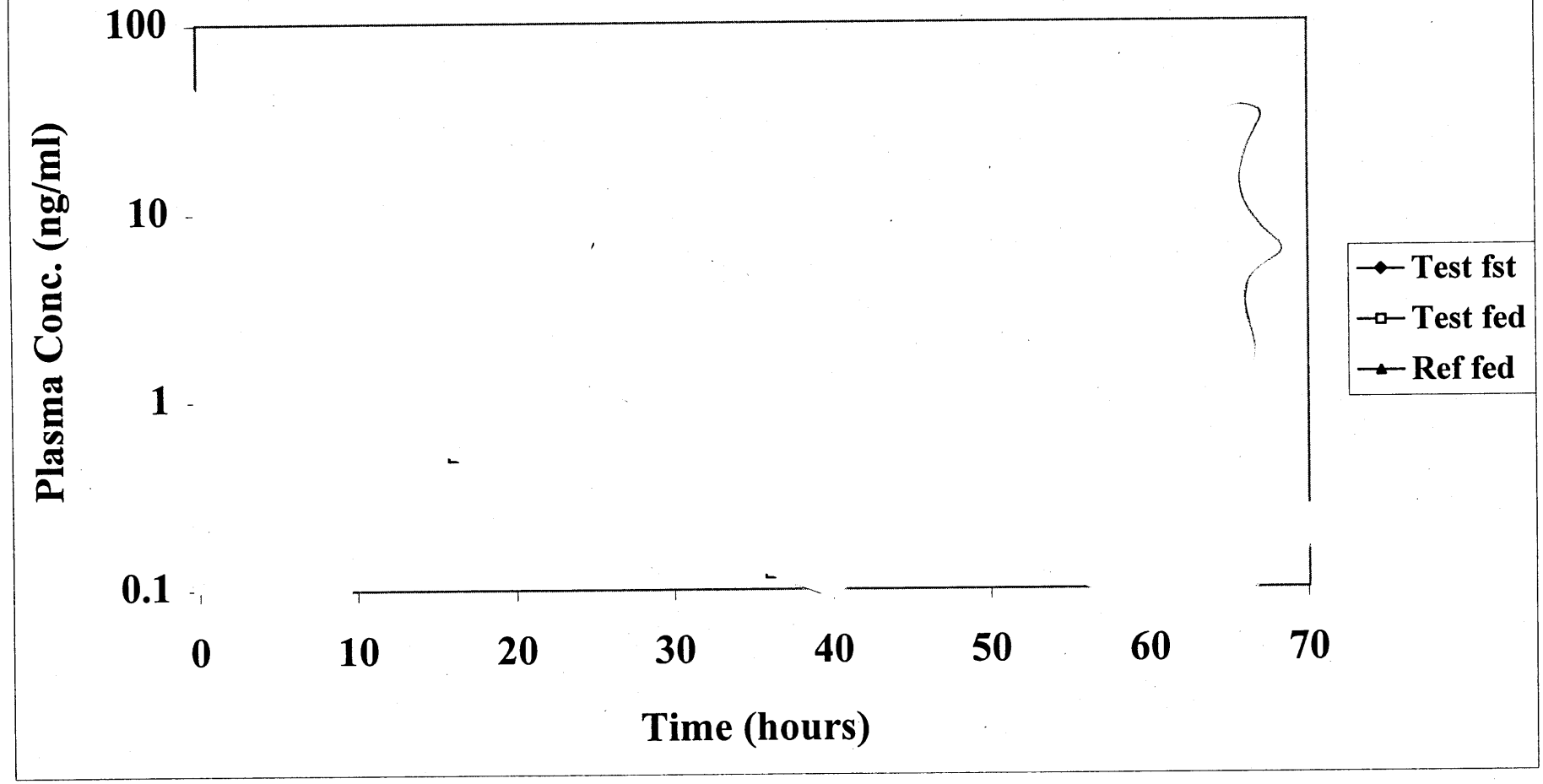


Figure 1

Mean Plasma Concentrations of Lovastatin, (Lovastatin, USP, 2x40 mg Tablets) under Fasting Conditions, Test (Trt A) vs Reference (Trt B)

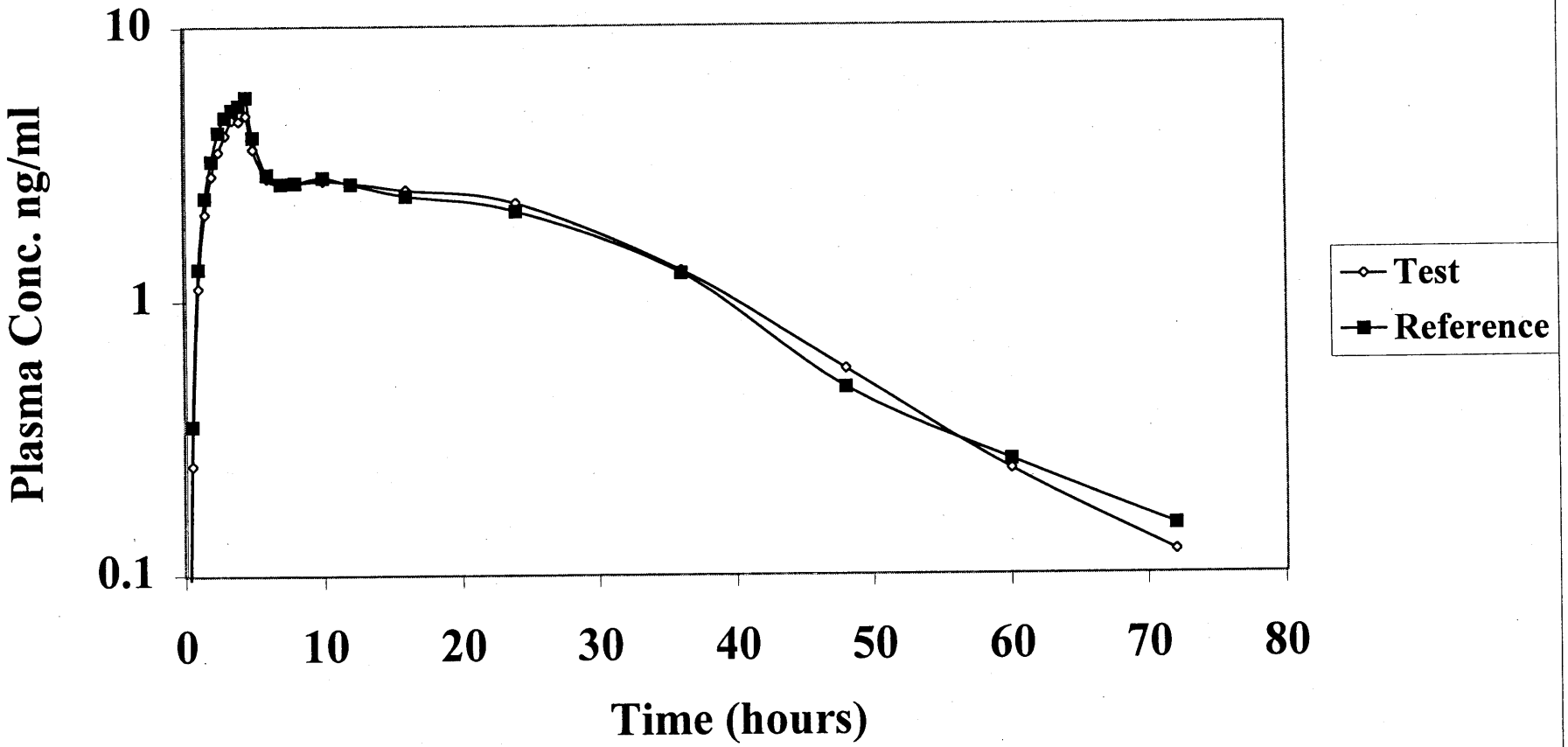


Figure 2

Mean Plasma Concentrations of beta-Hydroxy Lovastatin, (Lovastatin, USP, 2x40 mg Tablets) under Fasting Conditions, Test (Trt A) vs Reference (Trt B)

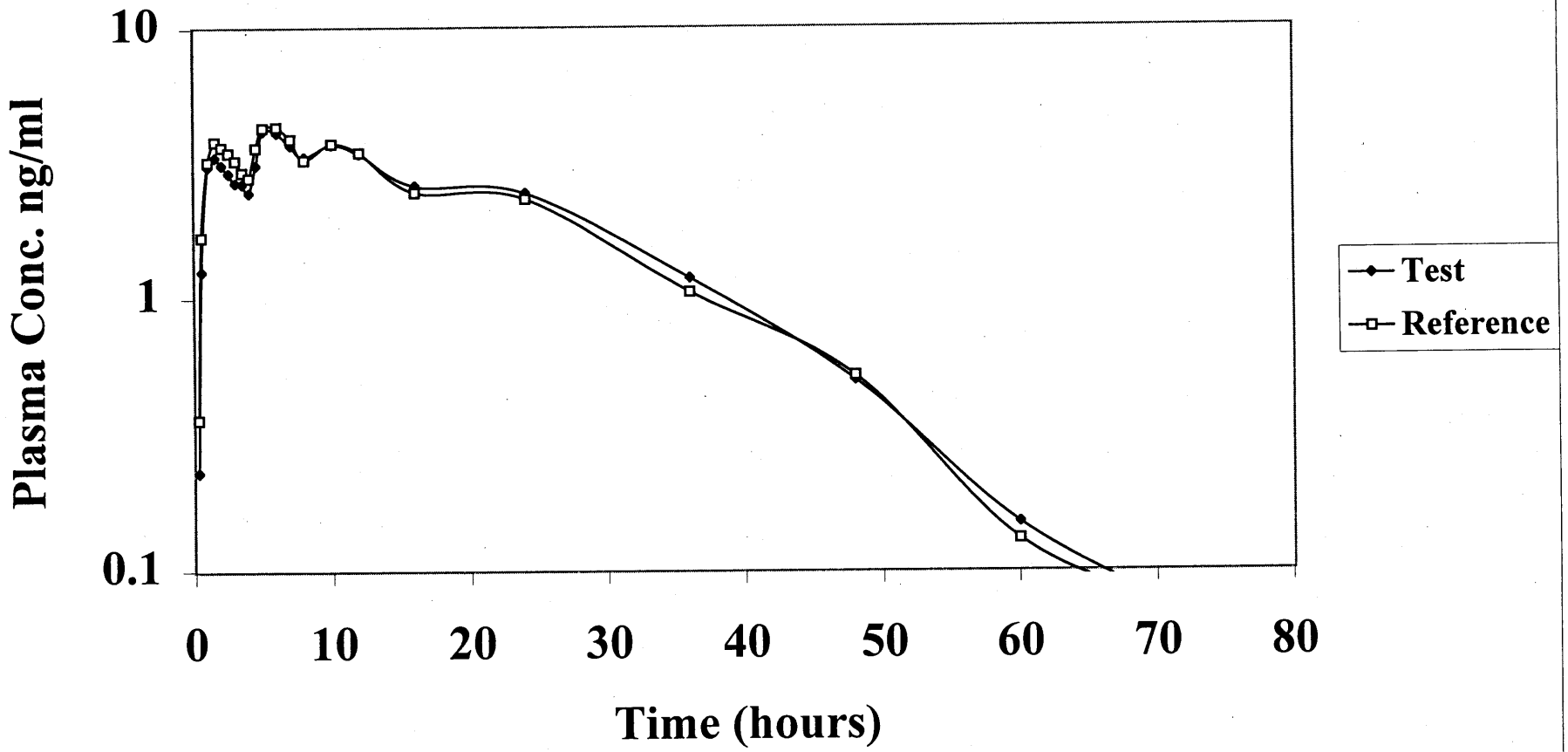
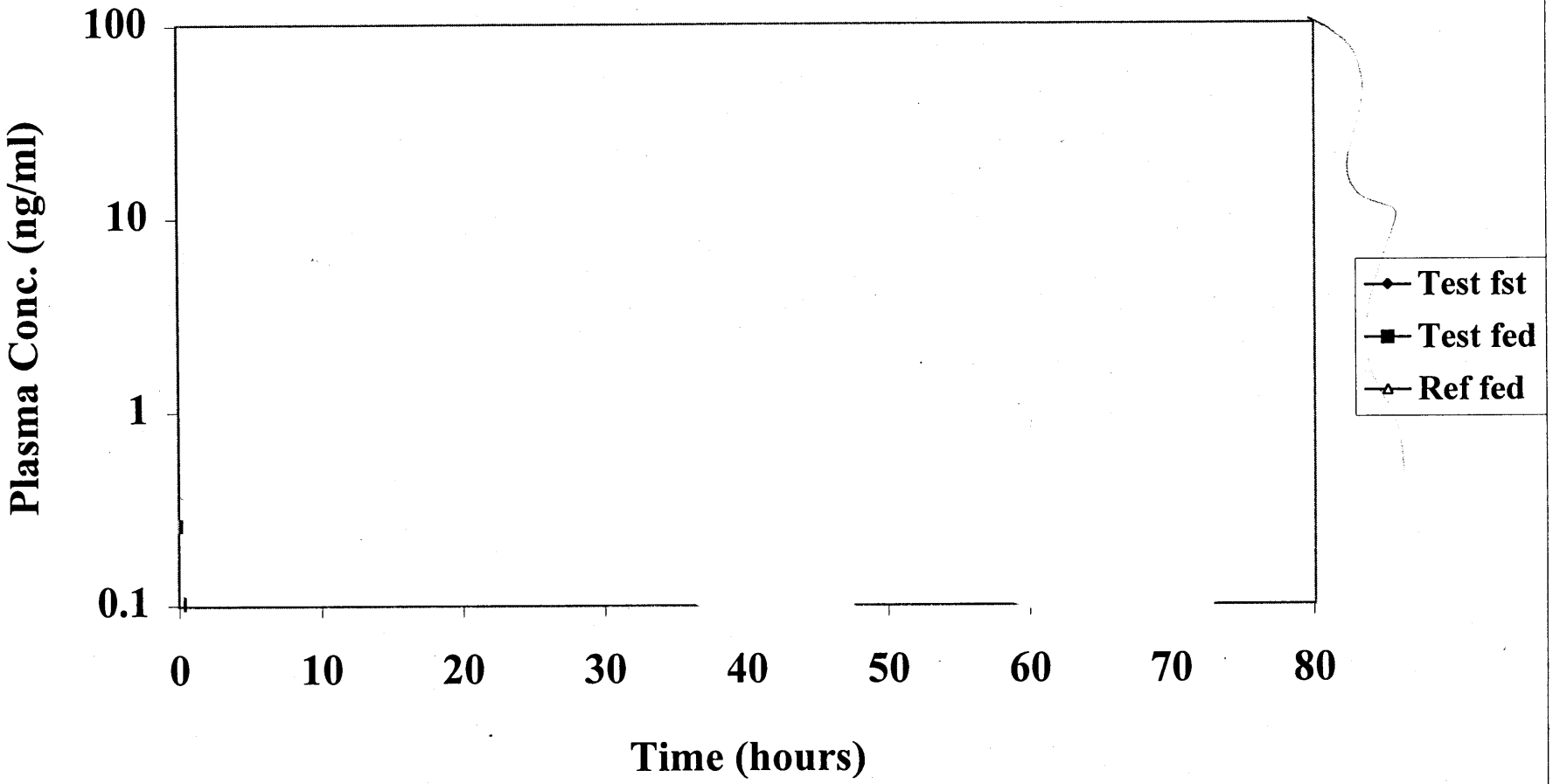


Figure 4

Plasma Concentrations of Beta-hydroxy lovastatin under Fed and Fasting Conditions after Oral Dose of 80 mg Lovastatin, USP, (Test) or Mevacor (Reference) Tablets (2x40 mg)



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-636

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY PACKAGE # 3

ANDA NUMBER: 75-636

FIRM: Eon Labs
227-15 N. Conduit Ave
Laurelton, NY 11413

DOSAGE FORM: Tablets

STRENGTH: 10 mg, 20 mg and 40 mg

DRUG: Lovastatin Tablets USP

CGMP STATEMENT/EIR UPDATED STATUS:
EER was found acceptable on 12/7/00.

BIO STUDY:
Bio status: Acceptable as of bio review signed off on 8-11-99.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
MV not required.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?
Containers used in the stability studies are identical to those listed in container section.

LABELING:
Labeling: Acceptable on 11/27/01.

STERILIZATION VALIDATION (IF APPLICABLE):
N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
Lot # 980611 and its size is ——— Tablets.

Source of NDS:
Referenced DMF # ——— was found adequate per review completed on 3-6-00 by this reviewer. New amendments do not need to be reviewed per Division policy.

APPEARS THIS WAY
ON ORIGINAL

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)

Exhibit batches for Lovastatin Tablets, 10mg and 20 mg and 40 mg lot # 980616 and 980615 and 980611, respectively and size of these batches [redacted], Tablets.

Exhibit/stability batch is manufactured via same manufacturing process.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

Intended production batch size for the drug product is [redacted] Tablets for all three strengths tablet.

Manufacturing process for the intended production size is identical to that used for the exhibit/bio/stability batch.

cc: ANDA 75-636

Endorsements:
HFD-625/MShaikh/
HFD-625/MSmela/

V:\firmsam\eon\ltrs&rev\75636app.sm3

/S/ - 11/28/01

/S/ 11/29/01

NDA 19-643/S-057

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

MAR 1 1999

Dear Dr. Hyman:

Please refer to your supplemental new drug application (S-057) dated November 6, 1998, received November 9, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70(c) for Mevacor (Lovastatin) tablets.

The supplemental application contains final printed labeling (#7825344) that will be implemented on or about June 1, 1999. Supplement-057 provides for changes in the CONTRAINDICATIONS, WARNINGS/ Skeletal Muscle and PRECAUTIONS/ Drug Interactions sections of the Mevacor package insert. These include:

1. Deletion of statements pertaining to [redacted] under CONTRAINDICATIONS, WARNING/Skeletal Muscle and PRECAUTIONS, Drug Interactions.

2. Revisions to the WARNINGS, PRECAUTIONS, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections. These include:

- **WARNINGS**
  The subsection "Skeletal Muscle" has been relocated ahead of the subsection " Liver Dysfunction".

- **WARNINGS, Skeletal Muscle**
  The entire skeletal muscle section has undergone extensive editorial revision.

- **PRECAUTIONS, Information for Patients**
  The phrase [redacted] has been deleted.

- **PRECAUTIONS, Drug Interactions**
  The term [redacted] has been replaced by "cyclosporine".

- **PRECAUTIONS,** [redacted]
  The phrase "(see WARNINGS, Skeletal Muscle)" has been added to the end of the paragraph.

- **ADVERSE REACTIONS, Laboratory Tests**
  The term [redacted] has been replaced by "creatine kinase".
  The acronym, [redacted], has been replaced by "CK".

- **ADVERSE REACTIONS, Concomitant Therapy and DOSAGE AND ADMINISTRATION**
  The term "[redacted]" has been replaced by "cyclosporine".

- **DOSAGE AND ADMINISTRATION, Concomitant Therapy**
  1. The heading has been revised to "Concomitant Lipid-Lowering Therapy".
  2. There is an updated revision regarding bile acid sequestrant.
  3. A maximum dosage recommendation of 20 mg of Mevacor has been included for patients receiving concomitant fibrates or niacin based on an analysis of myopathy and rhabdomyolysis during post-marketing surveillance.

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

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

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

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

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

Sincerely yours,

/S/ 12/8/97

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

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-636 **Date of Submission: May 14, 1999**
Applicant's Name: Eon Labs
Established Name: Lovastatin Tablets USP, 10 mg, 20 mg and 40 mg

Labeling Deficiencies:

1. CONTAINER (60's, 90's, 500's and 1000's)

   a. Satisfactory in draft.

2. INSERT

   a. GENERAL COMMENT

      Please note the most recent labeling for the reference listed drug, MEVACOR®, was approved March 1, 1999. Please revise your insert labeling to be in accord with the enclosed copy of this labeling.

   b. TITLE

      We encourage the inclusion of "Rx only" in this section.

Please revise your container labels and insert labeling, as instructed above, and submit 12 copies of final printed container labels for each strength and package size, along with 4 copies of draft insert labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

APPEARS THIS WAY
ON ORIGINAL

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-636

CORRESPONDENCE

Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

October 22, 2001
Michelle Dillahunt
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP
NC

General Correspondance

RE: Lovastatin Tablets, USP, 10 mg, 20 mg and 40 mg
ANDA 75-636

Dear Ms. Dillahunt:

The applicant, Eon Labs Manufacturing, Inc., acknowledges that a pediatric exclusivity expiring on September 11, 2002, has been granted to Merck and Company ,Inc. for Mevacor®, NDA 19-643.

We certify that Lovastatin tablets manufactured in conformance to the above mentioned application will not be marketed or distributed for this indication until after the expiration date of the exclusivity on September 11, 2002.

If there are any comments or questions about this application, please contact me at telephone (718) 276-8600, extension 343, facsimile (718) 276-8635.

Sincerely,
Eon Labs Manufacturing, Inc.

Amal Shaker
Sr. Regulatory Affairs Associate

CENTER FOR DRUG
OCT 23 2001
EVALUATION AND RESEARCH

APPEARS THIS WAY
ON ORIGINAL

ANDA 75-636

JUL 18 2001

Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 North Conduit Avenue
Laurelton, NY 11413

APPEARS THIS WAY ON ORIGINAL

Sent by Facsimile and U.S. Mail

Dear Ms. Ciganek:

This is in reference to your abbreviated new drug application (ANDA) for Lovastatin Tablets USP, 10 mg, 20 mg and 40 mg dated, May 14, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act. This letter is to inform you that the reference listed drug (RLD), Mevacor® (Lovastatin) Tablets USP, upon which you have based your application, is subject to a period of pediatric exclusivity which expires on December 15, 2001.

Pursuant to the June 22, 2001, Court Order entered by Judge James Robertson in Merck & Co., Inc. v. Food and Drug Administration, et. al., Civil Action No. 01-1343 (JR) in the U.S. District Court for the District of Columbia, the Pediatric Exclusivity Board's Memorandum of June 15, 2001, was vacated and remanded for further consideration. The Pediatric Exclusivity Board reconsidered its decision and on July 17, 2001, decided to grant pediatric exclusivity to Mevacor® (Lovastatin) Tablets USP. Therefore, the

Based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved.** This determination is based upon information available to the Agency at this time, i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug products, and is subject to change on the basis of new information that may come to our attention. Final approval cannot be granted earlier than December 15, 2001.

As noted in the current edition of the Agency's publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book), U.S. Patent number 4231938 ('938 patent) for the RLD, Mevacor® (Lovastatin), was scheduled to expire on June 15, 2001. Your application contains a Paragraph III Certification to the '938 patent under Section 505(j)(2)(A)(vii)(III) of the Act stating that your commercial manufacture, use, or sale of these drug products will not commence until the expiration of the patent.

However, Section 111 of Title I of the Food and Drug Administration Modernization Act of 1997 (FDAMA) created section 505(A) of the Federal Food , Drug and Cosmetic Act (21 U.S.C. 355a). Section 505A permits the sponsor of the new drug application for the RLD to obtain an additional six months of exclusivity if, in accord with the statute, the sponsor submits data previously requested by the Agency relating to the safe and effective use of the drug in a pediatric population. In this

case, the RLD holder, Merck, has submitted data to support the use of Mevacor® (Lovastatin) in a pediatric population. The Agency's Pediatric Exclusivity Board has determined that the data support the granting of 6 months of exclusivity to the RLD. Consequently, the awarding of this exclusivity will effectively lengthen the life of the patent referenced above by an additional 6 months. Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C 3255(j)(5)(B)(ii) of the Act until the additional exclusivity period granted to the RLD holder for the '938 patent has expired on December 15, 2001.

Because the Agency is granting a **tentative approval** for this application, when you believe that your application may be considered for final approval, you must amend your application to notify the Agency whether circumstances have or have not arisen that may affect the effective date of final approval. To reactivate your application, please submit an amendment at least 60 days (but not more than 90 days) prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as final printed labeling, chemistry, manufacturing, and controls data as appropriate. Please note that this amendment should be submitted even if none of these changes were made. The amendment should be designated clearly in your cover letter as a MINOR AMENDMENT. In addition to this amendment, the Agency may request at any time prior to the final date of approval that you submit an additional amendment containing the information described above. Any changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the application will be made. In addition to, or instead of, the amendments referred to above, the Agency may, at any time prior to the final date of approval, request that you submit amendments containing the information requested above.

The drug products that are the subject of this abbreviated application may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery or introduction into interstate commerce of this drug before the effective final approval date is prohibited under Section 501 of the Act. Also, until the Agency issues the final approval letter, these drug products will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

Please contact Cecelia Parise, R.Ph., Special Assistant for Regulatory Policy at (301) 827-5845, for further information regarding this issue.

Sincerely yours,

7/18/01

Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-636

JUL - 3 2001

Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 North Conduit Avenue
Laurelton, NY 11413

APPEARS THIS WAY
ON ORIGINAL

Sent by Facsimile and U.S. Mail

Dear Ms. Ciganek:

This is in reference to your abbreviated new drug application dated May 14, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Lovastatin Tablets USP, 10 mg, 20 mg and 40 mg.

[redacted]

Therefore, the drug products that are the subject of this abbreviated new drug application may not be marketed under Section 505 of the Act. You will receive further notice from the Agency that either the [redacted] The introduction or delivery for introduction of these drug products into interstate commerce before this occurs is prohibited under Section 501 of the Act.

If you have any questions, please contact Cecelia Parise, R.Ph. Special Assistant for Regulatory Policy, Office of Generic Drugs, at (301) 827-5845.

Sincerely,

/S/ 7/3/01

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure: Court Order dated June 22, 2001

ANDA 75-636

JUN 18 2001

Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 North Conduit Avenue
Laurelton, NY 11413

APPEARS THIS WAY
ON ORIGINAL

Sent by Facsimile and U.S. Mail

Dear Ms. Ciganek:

This is in reference to your abbreviated new drug application dated May 14, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Lovastatin Tablets USP, 10 mg, 20 mg and 40 mg.

Until the stay expires on Wednesday June 20, 2001, 11:59 p.m., or is extended or vacated by further order of the court, the drug products that are the subject of this abbreviated new drug application may not be marketed under Section 505 of the Act. The introduction or delivery for introduction of these drug products into interstate commerce before this occurs is prohibited under Section 501 of the Act.

If you have any questions, please contact Cecelia Parise, R.Ph. Special Assistant for Regulatory Policy, Office of Generic Drugs, at (301) 827-5845.

Sincerely,

/S/

6/18/01

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure: Court Order dated June 16, 2001

Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

July 12, 1999

Dale P. Conner, Pharm D.
Director
Division of Bioequivalence
Office of Generic Drugs, HFD-650
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
AB

TELEPHONE BIOEQUIVALENCY AMENDMENT

Re: ***Lovastatin Tablets, USP, 10 mg, 20 mg & 40 mg***
ANDA 75-636

Dear Dr. Conner:

Reference is made to the telephone call from FDA's Patty Nguyen, Project Manager and Mamata Gokhale, Reviewer from Division of Bioequivalence to Eon Labs Manufacturing Inc.'s Patricia Kaufold, Manager of Regulatory Affairs on July 9, 1999 for our Abbreviated New Drug Application, Lovastatin Tablets, USP, 10 mg, 20 mg and 40 mg, ANDA 75-636. Listed below are our responses to the two points that were discussed.

1. **Comment:** **There is a discrepancy in the expiration date of the RLD for the 40 mg tablet in Eon's CoA as compared to the Pharmacokinetics section of the bio study. For the RLD (Mevacor, 40 mg, lot # E1334) Eon's CoA states 10/98 as the expiration date and the Pharmacokinetics section of the bio study states 10/99 as the expiration date. Since they are the same lot #, they should be the same. Which is the correct date?**

   Response: The correct expiration date for the RLD, Mevacor Tablets, 40 mg, lot # E1334 is 10/99. We are providing corrected copies of Eon's CoA for the RLD ***(Attachment 1)***.

2. **Comment:** **Please provide the expiration dates of the RLD for the 10 mg and 20 mg tablets.**

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REC'D
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Response: The expiration date of Mevacor Tablets, 10 mg, lot # E1280 is 5/99 and the expiration date of Mevacor Tablets, 20 mg, lot # E8509 is 8/99.

If further information is needed or if there are additional questions, please do not hesitate to call me at 718-276-8607 extension 423.

Sincerely,
Eon Labs Manufacturing, Inc.

Patricia Kaufold
Patricia Kaufold
Manager, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Redacted 2

pages of trade secret and /or confidential commercial information

ANDA 75-636

APPEARS THIS WAY
ON ORIGINAL

Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 North Coduit Avenue
Laurelton, NY 11413

JUN 23 1999

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated June 11, 1999 and your faxed amendment dated June 14, 1999.

NAME OF DRUG: Lovastatin Tablets USP, 10 mg, 20 mg and 40 mg

DATE OF APPLICATION: May 14, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 17, 1999

We will correspond with you further after we have had the opportunity to review your application.

Please identify any communications concerning this application with the number shown above.

Should you have questions concerning this application contact:

Denise Huie
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Robert L. West, M.S., R.Ph.
Director,
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

mep

ack for filing 6/14/99 per FAX
ISI

APPEARS THIS WAY
ON ORIGINAL

NEW CORRESP
NC

June 14, 1999

Sandra Middleton
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

RE: **General Correspondance**
Lovastatin Tablets, USP, 10 mg, 20 mg and 40 mg ANDA 75-636

Dear Ms. Middleton:

The applicant, Eon Labs Manufacturing, Inc., acknowledges that an exclusivity for the primary prevention of coronary heart disease in patients without symptomatic cardiovascular disease who have average to moderately elevated Total - C and LDL-C and below average HDL-C expiring on March 11, 2002, has been granted to Merck and Company , Inc. for Mevacor®, NDA 19-643. A copy of the relevant page of the 19th edition of the "Orange Book" follows.

We certify that Lovastatin tablets manufactured in conformance to the above mentioned application will not be marketed or distributed for this indication until after the expiration date of the exclusivity on March 11, 2002. Furthermore, we have reviewed our proposed labeling for Lovastatin to ensure it does not include this indication.

If there are any comments or questions about this application, please contact me at telephone (718) 276-8600, extension 330, facsimile (718)276-8635.

Sincerely,
Eon Labs Manufacturing, Inc.

Sadie M. Ciganek

Sadie M. Ciganek
Vice President Regulatory Affairs

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JUN 15 1999
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Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

Acct for filing 6/11/99
505(j)(2)(A)

May 14, 1999

Douglas L. Sporn
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

APPEARS THIS WAY
ON ORIGINAL

RE: **Original ANDA - PAPER AND ELECTRONIC**
Lovastatin Tablets, USP, 10 mg, 20 mg and 40 mg

Dear Mr. Sporn:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act, enclosed is an original Abbreviated New Drug Application for Lovastatin Tablets, USP, 10 mg, 20 mg, and 40 mg. This application consists of the following volumes:

Volume 1	Debarment, patent and exclusivity certifications, Section 505(j)(2)(A) information, labeling, dissolution profiles, certificates of analysis, components and composition statements and raw material control data.
Volume 2	Manufacturing and packaging records including executed batch records.
Volume 3	Container/closure, finished product control, methods validation, stability data, control numbers, samples, and environmental impact statement.
Volume 4-31	Bio equivalence study summary and test results (also included are diskettes).

A full table of content precedes each appropriately paginated volume.

Please note that the electronic submission will be submitted separately within 30 days.

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MAY 17 1999
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We have also included an analytical methods validation package in a separate volume.

In addition to the archival and review copies, we are submitting a certified true copy of the chemistry, manufacturing and controls data to the District Field Office, Brooklyn, New York. Subsequent amendments or supplements containing chemistry, manufacturing and controls data will also be submitted to the District Field Office.

If there are any comments or questions about this application, please contact me at telephone (718) 276-8600, extension 330, facsimile (718)276-8635.

Sincerely,
Eon Labs Manufacturing, Inc.

Sadie M. Ciganek
Vice President Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL