CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-551

Generic Name:	Lovastatin Tablets USP, 10 mg, 20 mg, and 40 mg
Sponsor:	TEVA Pharmaceuticals USA
Approval Date:	December 17, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
75-551

CONTENTS

Reviews / Information Included in this ANDA Review.	
Approval Letter	X
Tentative Approval Letter	X
Final Printed Labeling	X
Medical Review(s)	
Chemistry Review(s)	X
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology & Biopharmaceutics Reviews	
Bioequivalence Review(s)	X
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-551

APPROVAL LETTER

ANDA 75-551

DEC 17 2001

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
PO Box 1090
North Wales, PA 19454

Dear Sir:

This is in reference to your abbreviated new drug application dated December 31, 1998, 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 March 24 and April 16, 1999; and September 18, October 24, and November 20, 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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-551

TENTATIVE APPROVAL LETTERS

ANDA 75-551

JUL 18 2001

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
PO Box 1090
North Wales, PA 19454

Sent by Facsimile and U.S. Mail

Dear Mr. Erickson:

This is in reference to your abbreviated new drug application (ANDA) for Lovastatin Tablets USP, 10 mg, 20 mg and 40 mg dated December 31, 1998, 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 final approval given to Teva Pharmaceuticals USA on June 15, 2001, for this application is hereby **withdrawn**.

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,

/S/ 7/18/2001

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

ANDA 75-551

SEP 30 1999

TEVA Pharmaceuticals USA
Attention: Deborah A. Jaskot
1510 Delp Drive
Kulpsville, PA 19443

Dear Madam:

This is in reference to your abbreviated new drug application dated December 31, 1998, 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 March 24, April 16, July 29, August 25, August 31, and September 22, 1999.

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 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 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 final-printed 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/ for

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

9/30/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-551

Final Printed Labeling

APPROVED

DEC 17 2001

R 5 78 13

Rev. E 11/2001

0324

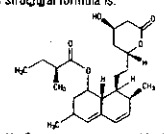
LOVASTATIN TABLETS USP

0528 0576 0528

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 [1 *S*-[1α(*R**), 3α, 7β, 8β (2 *S**, 4 *S**), 8aβ]]-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate. Its structural formula is:



$C_{24}H_{36}O_5$ M.W. 404.55

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

Lovastatin Tablets are supplied as 10 mg, 20 mg or 40 mg tablets for oral administration. In addition, each tablet contains the following inactive ingredients: lactose monohydrate, pregelatinized starch, magnesium stearate, and microcrystalline cellulose. Butylated hydroxyanisole (BHA) is added as a preservative. Lovastatin Tablets, 10 mg also contain FD&C Yellow #6. Lovastatin Tablets, 20 mg also contain FD&C Blue #1. Lovastatin Tablets, 40 mg also contain D&C Yellow #10, FD&C Blue #1, and FD&C Yellow #6.

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 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.

**Kaniola, 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 I.

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 [6.2 mmol/L-7.6 mmol/L], LDL-C>160 mg/dL [4.1 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. All changes in the lipid measurements (Table III) in lovastatin treated patients were dose-related and significantly different from placebo ($p \leq 0.001$). 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/TOTAL-C/ HDL-C (mean)	HDL-C (mean)	TG (median)
Placebo	1663	+0.7	+0.4	+2.0	+0.2	+0.5	+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 placebo alone ($p=0.001$). The predictive value of changes in IMT for stro
yet been established. In the lovastatin group there was a significant re
the number of patients with major cardiovascular events relative to th
group (5 vs.14) and a significant reduction in all-cause mortality (1 vs.

Eye

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

A three-year, double-blind, placebo-controlled study in hypercholes
patients to assess the effect of lovastatin on the human lens demonst
there were no clinically or statistically significant differences between the
and placebo groups in the incidence, type or progression of lenticular
There are no controlled clinical data assessing the lens available for
beyond three years.

INDICATIONS AND USAGE

Therapy with lovastatin should be a component of multiple risk factor in
In those individuals with dyslipidemia at risk for atherosclerotic vascula
Lovastatin should be used in addition to a diet restricted in saturated fat
lesterol as part of a treatment strategy to lower total-C and LDL-C to tar
when the response to diet and other nonpharmacological measures alone
inadequate to reduce risk.

Coronary Heart Disease

Lovastatin is indicated to slow the progression of coronary atherosc
patients with coronary heart disease as part of a treatment strategy to low
and LDL-C to target levels.

Hypercholesterolemia

Therapy with lipid-altering agents should be a component of multiple r
intervention in those individuals at significantly increased risk for arther
vascular disease due to hypercholesterolemia. Lovastatin is indicat
adjunct to diet for the reduction of elevated total-C and LDL-C levels i
with primary hypercholesterolemia (Types IIa and IIb***), when the res
diet restricted in saturated fat and cholesterol and to other nonpharma
measures alone has been inadequate.

General Recommendations

Prior to initiating therapy with lovastatin, secondary causes for hyp
terolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, neph
drome, dysproteinemias, obstructive liver disease, other drug therapy, alc
should be excluded, and a lipid profile performed to measure total-C, HD
TG. For patients with TG less than 400 mg/dL (<4.5 mmol/L), LDL-C can be
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 a
concentrations should be determined by ultracentrifugation. In hypertrigly
patients, LDL-C may be low or normal despite elevated total-C. In suc
lovastatin is not indicated.

The National Cholesterol Education Program (NCEP) Treatment Guide
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 Wh Consider Drug Th (mg/dL)
CHD† or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug opt
2+ Risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10-20% 10-year risk <10%
0-1 Risk factor†††	<160	≥160	≥190 (160-189: LDL-lo drug optiona

† CHD, coronary heart disease

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

††† Almost all people with 0-1 risk factor have a 10-year risk <10%; thus,
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, no
(total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL
are set 30 mg/dL higher than LDL-C goals for each risk category.

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

Since the goal of treatment is to lower LDL-C, the NCEP recommends tha
levels be used to initiate and assess treatment response. Only if LDL-C l
not available, should the total-C be used to monitor therapy.

Although lovastatin may be useful to reduce elevated LDL-C levels in patie
combined hypercholesterolemia and hypertriglyceridemia where hype
terolemia is the major abnormality (Type IIb hyperlipoproteinemia), it has
studied in conditions where the major abnormality is elevation of chylo
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 transa
(see **WARNINGS**).

Pregnancy and lactation. Atherosclerosis is a chronic process and the dis
ation of lipid-lowering drugs during pregnancy should have little impact on
come of long-term therapy of primary hypercholesterolemia. Moreover,
terol and other products of the cholesterol biosynthesis pathway are essen
ponents for fetal development, including synthesis of steroids and cell mem
Because of the ability of inhibitors of HMG-CoA reductase such as lova
decrease the synthesis of cholesterol, and possibly other products of the
terol biosynthesis pathway, lovastatin is contraindicated during pregnanc
nursing mothers. **Lovastatin should be administered to women of child
age only when such patients are highly unlikely to conceive.** If the
becomes pregnant while taking this drug, lovastatin should be discontinue
diately and the patient should be apprised of the potential hazard to the fe
PRECAUTIONS, *Pregnancy*).

WARNINGS

Skeletal Muscle

Lovastatin and other inhibitors of HMG-CoA reductase occasionally cause my
which is manifested as muscle pain or weakness associated with grossly
creatine kinase (> 10x the upper limit of normal [ULN]). **Rhabdomyolysis,
without acute renal failure secondary to myoglobinuria, has been r**

(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.

**Kaniola, 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 I.

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

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:

$$\text{LDL-C} = \text{total-C} - [0.2 \times (\text{TG}) + \text{HDL-C}]$$

For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In 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 judgment also may call for deferring drug therapy in this subcategory.

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

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

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

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the total-C be used to monitor therapy.

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

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 weeks, and 4 among 1649 patients randomized to 80 mg daily. When drug treatment was interrupted or discontinued in these patients, muscle symptoms and c atine kinase (CK) increases promptly resolved. The risk of myopathy is increas by concomitant therapy with certain drugs, some of which were excluded by EXCEL study design.

Myopathy caused by drug interactions.

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

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

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

Reducing the risk of myopathy.

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

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

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

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

In patients taking concomitant cyclosporine, fibrates or niacin, the dose lovastatin should generally not exceed 20 mg/day (see **DOSAGE AND ADMINIS TRATION** and **DOSAGE AND ADMINISTRATION**, *Concomitant Lipid-Lowerin Therapy*), as the risk of myopathy increases substantially at higher dose Concomitant use of lovastatin with itraconazole, ketoconazole, erythromycin clarithromycin, HIV protease inhibitors, nefazodone, or large quantities of grap fruit juice (>1 quart daily) is not recommended. If no alternative to a short cours of treatment with itraconazole, ketoconazole, erythromycin, or clarithromycin available, a brief suspension of lovastatin therapy during such treatment can b considered as there are no known adverse consequences to brief interruptions 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 least one year in early clinical trials (see ADVERSE REACTIONS). When the dru was interrupted or discontinued in these patients, the transaminase levels usuall fell slowly to pretreatment levels. The increases usually appeared 3 to 12 month after the start of therapy with lovastatin, and were not associated with jaundice other clinical signs or symptoms. There was no evidence of hypersensitivity: the EXCEL study (see **CLINICAL PHARMACOLOGY**, *Clinical Studies*), the incidenc 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 o lovastatin. However, in post-marketing experience with lovastatin, symptomati liver disease has been reported rarely at all dosages (see **ADVERSE REACTIONS**).

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

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

As with other lipid-lowering agents, moderate (less than three times the upper limi of normal) elevations of serum transaminases have been reported following therap with lovastatin (see **ADVERSE REACTIONS**). These changes appeared soon afte initiation of therapy with lovastatin, were often transient, were not accompanied b any symptoms and interruption of treatment was not required.

PRECAUTIONS

General

Lovastatin may elevate creatine phosphokinase and transaminase levels (se **WARNINGS** and **ADVERSE REACTIONS**). This should be considered in the differentia 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 hypercho lesterolemia, 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.

3A4 Interactions: Lovastatin has no CYP3A4 inhibitory activity; therefore, it is expected to affect the plasma concentrations of other drugs metabolized by 3A4. However, lovastatin itself is a substrate for CYP3A4. Potent inhibitors of 3A4 may increase the risk of myopathy by increasing the plasma concentration IMG-CoA reductase inhibitory activity during lovastatin therapy. These itors include cyclosporine, itraconazole, ketoconazole, erythromycin, clarmycin, HIV protease inhibitors, nefazodone, and large quantities of grapefruit (>1 quart daily) (see **CLINICAL PHARMACOLOGY**, *Pharmacokinetics* and **INGS**, *Skeletal Muscle*).

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

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

narin Anticoagulants: In a small clinical trial in which lovastatin was administered arfarin treated patients, no effect on prothrombin time was detected. However, ner HMG-CoA reductase inhibitor has been found to produce a less than twond increase in prothrombin time in healthy volunteers receiving low doses of arin. Also, bleeding and/or increased prothrombin time have been reported in patients taking coumarin anticoagulants concomitantly with lovastatin. It is mmended that in patients taking anticoagulants, prothrombin time be determined e starting lovastatin and frequently enough during early therapy to insure that gnificant alteration of prothrombin time occurs. Once a stable prothrombin has been documented, prothrombin times can be monitored at the intervals ly recommended for patients on coumarin anticoagulants. If the dose of tatin is changed, the same procedure should be repeated. Lovastatin therapy not been associated with bleeding or with changes in prothrombin time in nts not taking anticoagulants.

anolol: In normal volunteers, there was no clinically significant pharmacokinetic armacodynamic interaction with concomitant administration of single doses vastatin and propranolol.

in: In patients with hypercholesterolemia, concomitant administration of tatin and digoxin resulted in no effect on digoxin plasma concentrations.

Hypoglycemic Agents: In pharmacokinetic studies of lovastatin in hypercholoolemic non-insulin dependent diabetic patients, there was no drug interaction glipizide or with chlorpropamide (see **CLINICAL PHARMACOLOGY**, *Clinical es*).

crine Function

-CoA reductase inhibitors interfere with cholesterol synthesis and as such t theoretically blunt adrenal and/or gonadal steroid production. Results of al trials with drugs in this class have been inconsistent with regard to drug s on basal and reserve steroid levels. However, clinical studies have shown ovastatin does not reduce basal plasma cortisol concentration or impair al reserve, and does not reduce basal plasma testosterone concentration. ner HMG-CoA reductase inhibitor has been shown to reduce the plasma sterone response to HCG. In the same study, the mean testosterone response G was slightly but not significantly reduced after treatment with lovastatin 40 mg for 16 weeks in 21 men. The effects of HMG-CoA reductase inhibitors on fertility have not been studied in adequate numbers of male patients. The s, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown. nts treated with lovastatin who develop clinical evidence of endocrine dysfunction d be evaluated appropriately. Caution should also be exercised if an HMG-CoA tase inhibitor or other agent used to lower cholesterol levels is administered to nts also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) ay decrease the levels or activity of endogenous steroid hormones.

Toxicity

statin produced optic nerve degeneration (Wallerian degeneration of retinoulate fibers) in clinically normal dogs in a dose-dependent fashion starting at g/kg/day, a dose that produced mean plasma drug levels about 30 times higher the mean drug level in humans taking the highest recommended dose (as ured by total enzyme inhibitory activity). Vestibulocochlear Wallerian-like eration and retinal ganglion cell chromatolysis were also seen in dogs treated weeks at 180 mg/kg/day, a dose which resulted in mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

vascular lesions, characterized by perivascular hemorrhage and edema, nuclear cell infiltration of perivascular spaces, perivascular fibrin deposits ecrosis of small vessels, were seen in dogs treated with lovastatin at a dose mg/kg/day, a dose which produced plasma drug levels (C_{max}) which were 30 times higher than the mean values in humans taking 80 mg/day.

ar optic nerve and CNS vascular lesions have been observed with other drugs s class.

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

togenesis, Mutagenesis, Impairment of Fertility

21-month carcinogenic study in mice, there was a statistically significant se in the incidence of hepatocellular carcinomas and adenomas in both and females at 500 mg/kg/day. This dose produced a total plasma drug ure 3 to 4 times that of humans given the highest recommended dose of atin (drug exposure was measured as total HMG-CoA reductase inhibitory y in extracted plasma). Tumor increases were not seen at 20 and 100 mg/kg/day, that produced drug exposures of 0.3 to 2 times that of humans at the 80 mg/day

A statistically significant increase in pulmonary adenomas was seen in mice at approximately 4 times the human drug exposure. (Although mice given 300 times the human dose [HD] on a mg/kg body weight basis, plasma of total inhibitory activity were only 4 times higher in mice than in humans 80 mg of lovastatin.)

was an increase in incidence of papilloma in the non-glandular mucosa of the ch of mice beginning at exposures of 1 to 2 times that of humans. The glandular sa was not affected. The human stomach contains only glandular mucosa.

4-month carcinogenicity study in rats, there was a positive dose response nship for hepatocellular carcinogenicity in males at drug exposures en 2-7 times that of human exposure at 80 mg/day (doses in rats were 5, 180 mg/kg/day).

reased incidence of thyroid neoplasms in rats appears to be a response that en seen with other HMG-CoA reductase inhibitors.

nically similar drug in this class was administered to mice for 72 weeks at 0, and 400 mg/kg body weight, which resulted in mean serum drug levels ximately 3, 15, and 33 times higher than the mean human serum drug ntration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas ignificantly increased in high dose females and mid- and high dose males, maximum incidence of 90 percent in males. The incidence of adenomas of er was significantly increased in mid- and high dose females. Drug treatment gnificantly increased the incidence of lung adenomas in mid- and high dose and females. Adenomas of the Harderian gland (a gland of the eye of s) were significantly higher in high dose mice than in controls.

idence of mutagenicity was observed in a microbial mutagen test using strains of *Salmonella typhimurium* with or without rat or mouse liver metactivation. In addition, no evidence of damage to genetic material was noted *o vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mamcell forward mutation study, an *in vitro* chromosome aberration study in elis, 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; Teratogenic effects:
Pregnancy Category X
See **CONTRAINDICATIONS**.
Safety in pregnant women has not been established.

Lovastatin has been shown to produce skeletal malformations at plasma levels 40 times the human exposure (for mouse fetus) and 80 times the human exposure (for rat fetus) based on mg/m² surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in either species at multiples of 8 times (rat) or 4 times (mouse) based on surface area. No evidence of malformations was noted in rabbits at exposures up to 3 times the human exposure (dose of 15 mg/kg/day, highest tolerated dose).

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review[1] 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.

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**).

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

ADVERSE REACTIONS
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/m².

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

Until further experience is obtained, no specific treatment of overdosage with 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 drugs 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 or 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, 10 mg are available as light peach, round, flat beveled tablets debossed with "926" on the upper surface and "93" on the lower surface. Packaged in bottles of 60, 100 and 1000.

Lovastatin Tablets USP, 20 mg are available as light blue, round, flat beveled tablets, debossed with "576" on the upper surface and "93" on the lower surface. Packaged in bottles of 60, 100, 1000 and 12500.

Lovastatin Tablets USP, 40 mg are available as light green, round, flat beveled tablets, debossed with "928" on the upper surface and "93" on the lower surface. Packaged in bottles of 60, 100, 1000, and 12500.

Store between 5° and 30°C (41° and 86°F). Lovastatin Tablets must be protected from light.

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

Rx only

Manufactured By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Printed in USA
Rev. E 11/2001

75-551

AP

12/17/01

NDC 0093-0576-68

LOVASTATIN Tablets, USP **20 mg** APPROVED

Each tablet contains:
Lovastatin, USP 20 mg

℞ **only**

TEVA

Usual Dosage: See package insert for full prescribing information.

Store between 5° and 30°C (41° and 86°F). Lovastatin Tablets must be protected from light.

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

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

L19820

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

PG Iss. 7/99

N 3 0093-0576-68 3 00

JUN 15 2001

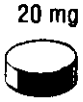
DEC 17 2001

NDC 0093-0576-10

LOVASTATIN Tablets, USP **20 mg** APPROVED

Each tablet contains:
Lovastatin, USP 20 mg

℞ **only**



TEVA

Usual Dosage: See package insert for full prescribing information.

Store between 5° and 30°C (41° and 86°F). Lovastatin Tablets must be protected from light.

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

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

L19819

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

PG Iss. 7/99

N 3 0093-0576-10 2

JUN 15 2001

DEC 17 2001

NDC 0093-0576-01

LOVASTATIN Tablets, USP **20 mg** APPROVED

Each tablet contains:
Lovastatin, USP 20 mg

℞ **only**

TEVA

Usual Dosage: See package insert for full prescribing information.

Store between 5° and 30°C (41° and 86°F). Lovastatin Tablets must be protected from light.

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

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

L19818

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

PG Iss. 7/99

N 3 0093-0576-01 0 00

JUN 15 2001

DEC 17 2001

75-551

AP 12/17/01

NDC 0093-0928-68

LOVASTATIN Tablets, USP 40 mg APPROVED

JUN 15 2001

Each tablet contains:
Lovastatin, USP 40 mg

℞ only

12500 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store between 5° and 30°C (41° and 86°F). Lovastatin Tablets must be protected from light.

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

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

L19824 PG Iss. 7/99

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 3 0093-0928-68 0 00

NDC 0093-0928-10

LOVASTATIN Tablets, USP 40 mg APPROVED

JUN 15 2001

Each tablet contains:
Lovastatin, USP 40 mg

℞ only

1000 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store between 5° and 30°C (41° and 86°F). Lovastatin Tablets must be protected from light.

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

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

L19823 PG Iss. 7/99

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 3 0093-0928-10 9 00

NDC 0093-0928-01

LOVASTATIN Tablets, USP 20 mg APPROVED

JUN 15 2001

Each tablet contains:
Lovastatin, USP 40 mg

℞ only

100 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store between 5° and 30°C (41° and 86°F). Lovastatin Tablets must be protected from light.

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

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

L19822 PG Iss. 7/99

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 3 0093-0928-01 7 00

NDC 0093-0928-06

LOVASTATIN Tablets, USP 40 mg

JUN 15 2001

Each tablet contains:
Lovastatin, USP 40 mg

℞ only

60 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store between 5° and 30°C (41° and 86°F). Lovastatin Tablets must be protected from light.

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

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

L19821 PG Iss. 7/99

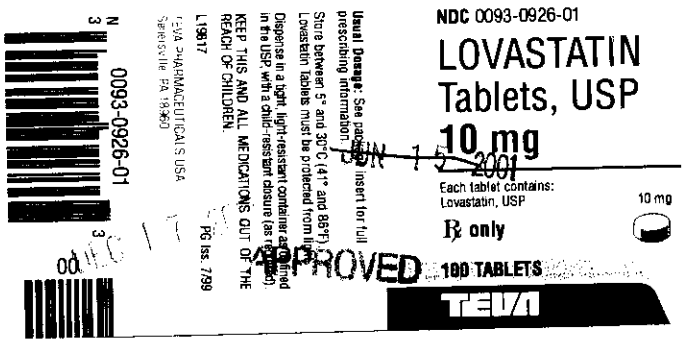
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

APPROVED

N 3 0093-0928-06 2 00

75-551

AP 12/17/01



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-551

CHEMISTRY REVIEW(S)

Office of Generic Drugs
Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO**: No. 1

2. **ANDA**: 75-551

3. **NAME AND ADDRESS OF APPLICANT**:
Teva Pharmaceuticals USA
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960

4. **LEGAL BASIS for ANDA SUBMISSION**: 505(j) and 21 CFR 314.92. Pursuant to Section 505(j)(2)(A)(vii)(III), U.S. Patent #4231938 will expire on June 15, 2001. One exclusivity (I-117) for the indication to slow the progression of coronary atherosclerosis in patients with coronary heart disease expired on February,8, 1998.

5. **SUPPLEMENT(s)**: N/A

6. **PROPRIETARY NAME**: Mevacor® Tablets; Merck & Co., Inc.

7. **NONPROPRIETARY NAME**: Lovastatin Tablets, USP

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

9. **AMENDMENTS AND OTHER DATES**:
TEVA:
12/31/98: Submission of ANDA (received on 12/31/98)
2/5/99: Withdrawal of the 60 count size of 10mg tablets
3/24/99: Bioequivalence Information

FDA:
2/9/99: Acknowledgment letter

10. **PHARMACOLOGICAL CATEGORY**: Antihypercholesterolemic Inhibitor

11. **HOW DISPENSED**: Rx

12. **RELATED IND/NDA/DMF(s)**:
DMF —
DMF —
DMF —

DMF [redacted]
DMF [redacted]
DMF [redacted]
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:** Oral Tablets

14. **Strength:** 10 mg, 20 mg. And 40 mg.

15. **CHEMICAL NAMES AND STRUCTURE:**
Generic name: Lovastatin
Chemical name: 1S-[1α(R*), 3α,7β,8β (2S*,4S*), 8aβ]]-1,2,3,7,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate.
Formula: $C_{24}H_{36}O_5$,
Molecular weight: 404.55
CAS registry number(s): 75330-75-5
Chemical structure:

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:**
1. Review of FPL found inadequate on 4/15/99.
2. Bio review has not yet been completed as of 6/7/99.
3. Validation of methods not required. Both Lovastatin drug substance and Lovastatin Tablets are USP.
4. EER was requested 2/9/99. Additional Analytical Testing Laboratories may need to be added at next cycle.

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Not approvable (FACSIMILE)

19. **REVIEWER:** Kenneth J. Furnkranz
DATE COMPLETED: 6/9/99

Redacted 21

pages of trade secret and/or confidential commercial information

Office of Generic Drugs
Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO**: No. 2

2. **ANDA**: 75-551

3. **NAME AND ADDRESS OF APPLICANT**:
Teva Pharmaceuticals USA
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960

4. **LEGAL BASIS for ANDA SUBMISSION**: 505(j) and 21 CFR 314.92.
Pursuant to Section 505(j)(2)(A)(vii)(III), U.S. Patent #4231938 will expire on June 15, 2001. One exclusivity (I-117) for the indication to slow the progression of coronary atherosclerosis in patients with coronary heart disease expired on February 8, 1998. An additional exclusivity (I-250) is covered in the 8/30/99 amendment.

5. **SUPPLEMENT(s)**: N/A

6. **PROPRIETARY NAME**: Mevacor® Tablets; Merck & Co., Inc.

7. **NONPROPRIETARY NAME**: Lovastatin Tablets, USP

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

9. **AMENDMENTS AND OTHER DATES**:

TEVA:

12/31/98:	Submission of ANDA (received on 12/31/98)
2/5/99:	Withdrawal of the 60 count size of 10mg tablets
3/24/99:	Bioequivalence Information
4/16/99	Bioequivalence information submitted
7/29/99	ANDA Amendment (response to Chemistry N/A FAX dated 6/29/99
8/25/99	ANDA Amendment (Labeling)
8/30/99	Exclusively Amendment
8/31/99	ANDA Amendment (response to Chemistry N/A Telephone call)

FDA:

2/9/99:	Acknowledgment letter
4/14-15/99	Labeling review
5/27/99	Bioequivalence Review

6/29/99	N/A FACSIMILE Amendment (chemistry, Labeling, Bioequivalence
8/25/99	Request for Telephone Amendment (Refer to the telecon dated 8/25/99 in the ANDA)

10. **PHARMACOLOGICAL CATEGORY:** Antihypercholesterolemic Inhibitor

11. **HOW DISPENSED**: Rx

12. **RELATED IND/NDA/DMF(s):**

DMF-
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

13. **DOSAGE FORM:** Oral Tablets

14. **Strength**: 10 mg, 20 mg. And 40 mg.

15. **CHEMICAL NAMES AND STRUCTURE:**

Generic name: Lovastatin
Chemical name: 1S-[1α(R*), 3α,7β,8β (2S*,4S*), 8aβ]]-1,2,3,7,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate.
Formula: $C_{24}H_{36}O_5$,
Molecular weight: 404.55
CAS registry number(s): 75330-75-5
Chemical structure:

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS**:

1. Current labeling was reviewed and deficiencies were noted and FAX'ed to the firm on 8/12/99. Response of 8/25/99 is acceptable (per telecon with T.Watkins of Labeling Review Branch and review dated 8/31/99.
2. TEVA's revised ———— specifications are Acceptable.
3. EER update was prepared 8/17/99 to include additional test labs. Awaiting acceptable EER at this time.

18. **CONCLUSIONS AND RECOMMENDATIONS**:

Approval pending acceptable EER.

19. **REVIEWER**: Kenneth J. Furnkranz

DATE COMPLETED: 9/7/99

Redacted 16

pages of trade secret and/or

confidential

commercial

information

6/29/99 JMC

Redacted 2

pages of trade secret and/or

confidential

commercial

information

Chemistry Closed

Office of Generic Drugs
Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO**: No. 3

2. **ANDA**: 75-551

3. **NAME AND ADDRESS OF APPLICANT**:
Teva Pharmaceuticals USA
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960

4. **LEGAL BASIS for ANDA SUBMISSION**: 505(j) and 21 CFR 314.92.
Pursuant to Section 505(j)(2)(A)(vii)(III), U.S. Patent #4231938 will expire on June 15, 2001. One exclusivity (I-117) for the indication to slow the progression of coronary atherosclerosis in patients with coronary heart disease expired on February 8, 1998. An additional exclusivity (I-250) is covered in the 8/30/99 amendment.

5. **SUPPLEMENT(s)**: N/A

6. **PROPRIETARY NAME**: Mevacor® Tablets; Merck & Co., Inc.

7. **NONPROPRIETARY NAME**: Lovastatin Tablets, USP

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

9. **AMENDMENTS AND OTHER DATES**:

TEVA:

12/31/98:	Submission of ANDA (received on 12/31/98)
*11/20/00	ANDA Major Amendment (new package sizes)
*3/23/01	ANDA Minor Amendment (minor changes; components & labeling)

FDA:

2/9/99:	Acknowledgment letter
4/14-15/99	Labeling review
5/27/99	Bioequivalence Review
6/29/99	N/A FACSIMILE Amendment (chemistry, Labeling, Bioequivalence
8/25/99	Request for Telephone Amendment (Refer to the telecon dated 8/25/99 in the ANDA)
9/30/99	ANDA Tentative Approval

* - Subject of the current review.

10. **PHARMACOLOGICAL CATEGORY:** Antihypercholesterolemic Inhibitor

11. **HOW DISPENSED:** Rx

12. **RELATED IND/NDA/DMF(s):**

DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —

13. **DOSAGE FORM:** Oral Tablets

14. **Strength:** 10 mg, 20 mg & 40 mg.

15. **CHEMICAL NAMES AND STRUCTURE:**
Generic name: Lovastatin
Chemical name: 1S-[1α(R*), 3α,7β,8β (2S*,4S*), 8aβ]]-1,2,3,7,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate.
Formula: $C_{24}H_{36}O_5$ Molecular weight: 404.55
CAS registry number(s): 75330-75-5

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:**
1. Labeling submitted in the 11/20/00 ANDA MAJOR Amendment was reviewed and revisions were requested. TEVA submitted revised labels and labeling in the 3/23/01 ANDA MINOR Amendment. Labeling is currently under review.
2. TEVA's new packages for the 10 mg, and 20 mg strength are acceptable.
3. CMC Revisions indicated in the 3/23/01 ANDA Amendment are acceptable.
4. EER update satisfactory as per EER of 9/30/99.

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Chemistry Closed pending Labeling review.

19. **REVIEWER:** Kenneth J. Furnkranz **DATE COMPLETED:** 5/2/01 **DATE REVISED:** 5/9/01

Labeling acceptable as is 6/15/01
6/15/01

Redacted 13

pages of trade secret and/or

confidential

commercial

information

Office of Generic Drugs
Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO**: No. 4 2. **ANDA**: 75-551

3. **NAME AND ADDRESS OF APPLICANT**:
Teva Pharmaceuticals USA
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960

4. **LEGAL BASIS for ANDA SUBMISSION**: 505(j) and 21 CFR 314.92.
Pursuant to Section 505(j)(2)(A)(vii)(III), U.S. Patent #4231938 will expire on June 15, 2001. One exclusivity (I-117) for the indication to slow the progression of coronary atherosclerosis in patients with coronary heart disease expired on February 8, 1998. An additional exclusivity (I-250) is covered in the 8/30/99 amendment. Pediatric Exclusivity expires on 12/15/01.

5. **SUPPLEMENT(s)**: N/A

6. **PROPRIETARY NAME**: Mevacor® Tablets; Merck & Co., Inc.

7. **NONPROPRIETARY NAME**: Lovastatin Tablets, USP

9. **AMENDMENTS AND OTHER DATES**:

TEVA:

12/31/98:	Submission of ANDA (received on 12/31/98)
11/20/00	ANDA Major Amendment (new package sizes)
3/23/01	ANDA Minor Amendment (minor changes; components & labeling)
6/13/01	Labeling Amendment
6/14/01	Labeling Amendment
*9/18/01	ANDA Minor Amendment

FDA:

2/9/99:	Acknowledgment letter
4/14-15/99	Labeling review
5/27/99	Bioequivalence Review
6/29/99	N/A FACSIMILE Amendment (chemistry, Labeling, Bio.)
8/25/99	Request for T/A (Refer to the 8/25/99 telecon in the ANDA)
9/30/99	ANDA Tentative Approval
5/10/01	Chemistry Closed (C.R. #3)
5/31/01	Labeling Approval Summary
6/15/01	Revised Labeling Approval Summary
6/15/01	ANDA Approval
6/18/01	ANDA Approval Stayed

7/3/01 Denial of Exclusivity remanded back to Agency
7/18/01 Full Approval Withdrawn. ANDA is Tentatively Approved until expiration of Pediatric Exclusivity (12/15/01)
* - Subject of the current review.

10. **PHARMACOLOGICAL CATEGORY:** Antihypercholesterolemic Inhibitor

11. **HOW DISPENSED:** Rx

12. **RELATED IND/NDA/DMF(s):**
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —

13. **DOSAGE FORM:** Oral Tablets 14. **Strength:** 10 mg, 20 mg & 40 mg.

15. **CHEMICAL NAMES AND STRUCTURE:**
Generic name: Lovastatin
Chemical name: 1S-[1α(R*), 3α,7β,8β (2S*,4S*), 8aβ]]-1,2,3,7,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate.
Formula: $C_{24}H_{36}O_5$ Molecular weight: 404.55
CAS registry number(s): 75330-75-5

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:**
1. CMC changes are Acceptable. ANDA is adequate for Tentative Approval.
2. A new Approval Summary is not necessary. No significant changes in the ANDA submission have occurred since the previous summary was prepared on 6/15/01.

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Tentative Approval (due to pediatric exclusivity until 12/15/01) or hold for full approval.

19. **REVIEWER:** Kenneth J. Furnkranz **DATE COMPLETED:** 10/03/01 **DATE REVISED:**

Redacted 4

pages of trade secret and/or

confidential

commercial

information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-551

BIOEQUIVALENCE REVIEW

(2)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 75-551 SPONSOR: Teva Pharmaceuticals USA

DRUG AND DOSAGE FORM: Lovastatin Tablets

STRENGTH(S): 10 mg, 20mg and 40 mg

TYPES OF STUDIES: Bioequivalence Studies under Fasting and Fed Conditions

CLINICAL STUDY SITE(S) ———

ANALYTICAL SITE(S): Same as above

STUDY SUMMARY: Bioequivalence Studies conducted under fasting and fed conditions were acceptable.

DISSOLUTION: Dissolution testing using USP method was acceptab

DSI INSPECTION STATUS

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

PRIMARY REVIEWER: (NAME) BRANCH: I

INITIAL: /s/ DATE 10/5/99

TEAM LEADER: (NAME) BRANCH:

INITIAL: /s/ DATE: 5/10/99

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

INITIAL: /s/ DATE: 5/27/99

The Studies were discussed with the director who concurred with the recommendation /s/ 5/27/99

V:\ division \ bio \ signoff.doc

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:75-551 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Lovastatin Tablets, 10.mg, 20 mg, and 40 mg

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

The dissolution testing conducted using USP dissolution method will need to be incorporated into your stability and quality control programs.

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

RECORD OF TELEPHONE CONVERSATION

On this date, I contacted Mr. Phillip Ericson to advise Teva Pharmaceuticals USA that Merck filed a temporary restraining order with the court on Friday, June 15, 2001 re: FDA's approval of generic Lovastatin. Arguments were heard on Saturday, June 16, 2001. The judge hearing this case, Judge Robertson, wanted to hear further arguments Tuesday at 4:00pm. Until then, Judge Robertson issued a temporary restraining order on Friday, June 15, requiring FDA to stay the approval of this product until Wednesday, 11:59pm, June 20, 2001.

I also advised Mr. Erickson to contact Kim Dettelbach at 301-827-1148 should he have any questions about the hearing (i.e., location of hearing, etc).

NOTE: Teva is not prepared to market at this time.

DATE
June 18, 2001

APPLICATION NUMBER
75-551

TELECON

INITIATED BY Pat Beers Block

PRODUCT NAME
Lovastatin Tablets USP, 10 mg, 20mg, and 40 mg strengths

FIRM NAME
Teva Pharmaceuticals USA

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Phillip Erickson

TELEPHONE NUMBER
215-591-3141

SIGNATURE
Pat Beers Block

/S/

6/18/01

Orig: ANDA 75-551
Cc: Division File
Chem. I telecon binder

v:\firmsnz\teva\telecons\75555lov

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 75-551

FIRM: Teva Pharmaceuticals, USA.
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960

DOSAGE FORM: Tablet

STREGHTH: 10, 20 and 40 mg

DRUG: Lovastatin

CGMP STATEMENT/EIR UPDATED STATUS: Satisfactory. An EER was issued for the indicated firms on 12/31/98, and was found Acceptable on 9/30/99 as per S. Ferguson of HFD-324.

Manufacturing, processing, packaging, labeling, and testing of the referenced drug product will be performed at:

Teva Pharmaceuticals
650 Cathill Road
Sellersville, PA 18960

The Lovastatin Drug Substance is [redacted]

The [redacted]. DMF # [redacted] was most recently reviewed for LovastatinTablets by HFD-625 and found satisfactory on 3/6/00.

The packaged and labeled product will be distributed by Teva USA through its warehouse/Distribution center at:

Teva Pharmaceuticals USA
151 Demorah Drive
Montgomeryville, PA 18963

Teva lists the following [redacted], that they may wish to utilize for

In addition, the following [redacted] may be utilized in the future as alternates to TEVA Pharmaceuticals USA's laboratory:

[redacted]

Teva has indicated that each of the listed [redacted] may perform the following testing:

Lovastatin USP	Full Testing
Lactose Monohydrate, NF	Full Testing
Pregelatinized Starch NF	Full Testing
Microcrystalline Cellulose NF:	Full Testing
FD&C Yellow #6 Aluminum Lake;	Full Testing
Butlyated Hydroxyanisole NF;	Full Testing
[redacted]	Full Testing
[redacted]	Full Testing
Magnesium Stearate NF:	Full Testing
Lovastatin Tablets USP	Release and/or Stability Testing

BIOEQUIVALENCY STATUS: Satisfactory. Office level Bioequivalence signoff occurred on 5/27/99.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Method validation by the District Laboratory is not required for the approval of the application. Teva Pharmaceutical USA has submitted methods for assay/impurities in the drug substance and drug product. The USP methods will be the regulatory methods. Teva has performed validation studies on the analytical methods and has determined the methods to be adequate for their intended use.

The stability indicating nature of the —— Method has been assessed by stress testing of the drug product. ——— testing was performed.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?

Teva has provided adequate information on the container/closure components utilized for packaging each of the three strengths of the drug product. Each of the strengths will be packaged into various systems and various fills, but will encompass package sizes of 60's, 100's, 1000's and 12500's. Refer to the updated table in the Chemistry Review #3 for complete information on the c/c systems utilized by Teva.

Package Sizes	Tablet Strengths		
	10 mg	20 mg	40 mg
60's	Yes	Yes	Yes
100's	Yes	Yes	Yes
1000's	Yes	Yes	Yes
12500's	No	Yes	Yes

* the c/c system utilized for the packaging of the commercial production batches is provided in Chemistry Review #1 and Chemistry Review #3.

LABELING: The final printed labeling is acceptable as of 6/14/01

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
Teva has submitted the original Batch Manufacturing Record for Lovastatin Tablets. The bio batch; Lot #Rx-0554-141, manufactured 8/3/98 is ——— tablets. The production batch size will also be ——— tablets. Satisfactory.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?): The exhibit batch for the Lovastatin Tablets 40 mg was used in the bioequivalence studies as well as the stability studies.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY? The production batch sizes for the Lovastatin tablets

USP 10, 20 and 40 mg are as follows:

Tablet Strength	Lot #	Batch size
10 mg	Rx-0554-176	[redacted] tablets
20 mg	Rx-0972-063	[redacted] tablets
40 mg	Rx-0554-141	[redacted] tablets

The manufacturing batch size and process for the production batches batches are the same as the exhibit batches.

cc: ANDA #75-551
HFD-600/Reading File
Endorsements:
HFD-625/K.Furnkranz/6/13/01
HFD-625/M.Smela, TL/6/13/01
V:\firmsnz\teva\ltrs&rev\75551app.sum.kjf.doc
F/T by: DJ 6/14/01
Approval Summary

/S/ 6/14/01

/S/ 6/15/01

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

ANDA Number: 75-551 **Date of Submission: June 14, 2001**
Applicant's Name: Teva Pharmaceuticals
Established Name: Lovastatin Tablets USP, 10 mg, 20 mg, and 40 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have 12 Final Printed Labels and Labeling? Yes
Container Labels: **10 mg** (100's) , **20 mg** (100's, 1000's and 12,500's), **40 mg** (60's, 100's, 1000's, and 12,500's) Satisfactory as of July 29, 1999 submission. In addition, **10 mg** (60 and 1000s), **20 mg** (60s) – Satisfactory in FPL submitted March 23, 2001 (attachment 6).
Professional Package Insert Labeling: Rev. C6/2001 vol 4.1 submitted June 14, 2001.
Post approval changes needed: none
Note: **DO NOT APPROVE THE JUNE 13, 2001 INSERT LABELING.**
BASIS OF APPROVAL:

Patent Data For NDA 19-643

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4231938	June 15, 2001		For hypocholesteremic fermentation products and process of preparation	P-III	Use

Exclusivity Data For NDA 19-643

Code/sup	Expiration	Description	Labeling impact
I-250/ s-055	March 11, 2002.	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.	Carved out

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: MEVACOR®
NDA Number: 19-643
NDA Drug Name: Lovastatin Tablets USP, 10 mg, 20 mg, & 40 mg
NDA Firm: Merck & Co.
Date of Approval of NDA Insert and supplement #: S-059/August 22, 2000 & S-062/64/April 26, 2001
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side by side comparison w/RLD labels in jacket.
Basis of Approval for the Carton Labeling: Side by side comparison w/RLD cartons in jacket.
Other Comments: S-055 was approved after S-057 on March 11, 1999, but is subject to exclusivity until March 11, 2002.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	

Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		x	
		x	

Failure to list dyes in Imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. The RLD is MEVACOR® (Merck; NDA 19-643/S-059/August 22, 2000 & S-062/64/April 26, 2001). S-055 was approved March 11, 1999 but is covered by exclusivity until March 11, 2002. Patent/Exclusivity – see above.
2. Patents/Exclusivities:
   There is one patent that exists for this drug product:
   4231938-Expires on June 15, 2001 – For Hypocholesteremic Fermentation Products and Process of Preparation.
   There are two exclusivities that exist:
   I-250 / S-055– Expires March 11, 2002 – Primary prevention of coronary heart disease in pt without symptomatic cardiovascular disease who have average to moderately elevated total-C and LDL-C and below average HDL-C.
   I-117 – Expired on February 8, 1998 – To slow progression of coronary atherosclerosis in patients with Coronary Heart Disease.
   See Vol. 1.1, pages 11-12.
3. The product is manufactured by Teva Pharmaceuticals USA, 650 Cathill Road, Sellersville, PA 18960. See Vol. 1.14, page 6097.
4. [redacted]. See Vol. 1.14, page 6102.
5. Container/Closure: See Vol. 1.15, pages 6479-6480.
6. Finished Product
   A white, nonhygroscopic crystalline powder that is insoluble in water and sparingly soluble in ethanol, methanol, and acetonitrile. See Vol. 1.1, page 31.
7. Product Line
   10 mg-light peach, round flat, beveled tablets debossed with "926" on the upper surface and "93" on the lower surface. Packaged in bottles of 60 crc,100, 1000.
   20mg-light blue, round flat, beveled tablets debossed with "576" on the upper surface and "93" on the lower surface. Packaged in bottles of 60 crc, 100, 1000, and 12,500.
   40mg-light green, round flat, beveled tablets debossed with "928" on the upper surface and "93" on the lower surface. Packaged in bottles of 60, 100, 1000, 12,500.
   See Vol. 1.1, page 53.
8. Component/Composition
   Innovator:
   Active: Lovastatin 10 mg, 20 mg, or 40 mg
   Inactive: Cellulose
   Lactose
   Magnesium Stearate
   Starch
   Butylated hydroxyanisole (preservative)
   10mg only-Red ferric oxide
   yellow ferric oxide
   20mg only-FD&C Blue 2
   40mg only-D&C Yellow 10
   FD&C Blue 2

   Applicant:
   Active: Lovastatin 10 mg, 20 mg, or 40 mg
   Inactive: Lactose monohydrate
   Pregelatinized Starch
   Microcrystalline cellulose
   Butylated Hydroxyanisole (preservative)
   [redacted]
   Magnesium stearate
   10mg only-FD&C Yellow #6
   20mg only-FD&C Blue #1
   40mg only-[redacted]

See Vol. 1.14, page 5854.

9. Storage/Dispensing

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

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

See Vol. 1.1, page 53.

Date of Review: June 14, 2001 **Date of Submission: June 14, 2001**

---

cc:

ANDA: 75-551
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
V:\FIRMSNZ\TEVA\LTRS&REV\75551ap.L
Review

/S/ 6/14/01
/S/ 6/15/2001

APPEARS THIS WAY
ON ORIGINAL

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

1/1

ANDA Number: 75-551 **Date of Submission: December 31, 1998**

Applicant's Name: Teva Pharmaceuticals

Established Name: Lovastatin Tablets USP, 10 mg, 20 mg, and 40 mg

Labeling Deficiencies:

1. GENERAL COMMENTS:

2. CONTAINER (10 mg-60's and 100's, 20 mg-100's, 1000's and 12,500's, 40 mg-60's, 100's, 1000's, and 12,500's)

   a. Please note that the Office of Generic Drugs does not normally approve bulk container labels.

   b. We encourage you to differentiate between product strengths, using color, shading, or other means, on your final printed labels.

   c. Please ensure that the established name is prominent on your final printed labels.

3. INSERT

   a. See comment (a) under container.

   b. 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.

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.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

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

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: MEVACOR®

NDA Number: 19-643/S-055
NDA Drug Name: Lovastatin Tablets USP, 10 mg, 20 mg and 40 mg
NDA Firm: Merck & Co.

Date of Approval of NDA Insert and supplement #: March 1, 1999/S-057
Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No
If yes, give date of labeling guidance:

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.	X		
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. The reference listed drug for this product is MEVACOR®(Merck; NDA#19-643/S-057; Approved March 1, 1999).

2. Patents/Exclusivities:

   There is one patent that exists for this drug product:

   4231938-Expires on June 15, 2001 - For Hypocholesteremic Fermentation Products and Process of Preparation.

   There are two exclusivities that exist:

   I-250 - Expires March 11, 2002 -

   I-117 - Expired on February 8, 1998 - To slow progression of coronary atherosclerosis in patients with Coronary Heart Disease.

   See Vol. 1.1, pages 11-12.

3. The product is manufactured by Teva Pharmaceuticals USA, 650 Cathill Road, Sellersville, PA 18960. See Vol. 1.14, page 6097.

4. [redacted]; See Vol. 1.14, page 6102.

5. Container/Closure:

   See Vol. 1.15, pages 6479-6480.

6. Finished Product

   A white, nonhygroscopic crystalline powder that is insoluble in water and sparingly soluble in ethanol, methanol, and acetonitrile. See Vol. 1.1, page 31.

7. Product Line

10 mg-light peach, round flat, beveled tablets debossed with "926" on the upper surface and "93" on the lower surface. Packaged in bottles of 60 and 100.

20mg-light blue, round flat, beveled tablets debossed with "576" on the upper surface and "93" on the lower surface. Packaged in bottles of 100, 1000, and 12,500.

40mg-light green, round flat, beveled tablets debossed with "928" on the upper surface and "93" on the lower surface. Packaged in bottles of 60, 100, 1000, 12,500.

See Vol. 1.1, page 53.

8. Component/Composition

Innovator:
Active: Lovastatin 10 mg, 20 mg, or 40 mg
Inactive: Cellulose
Lactose
Magnesium Stearate
Starch
Butylated hydroxyanisole (preservative)
10mg only-Red ferric oxide
yellow ferric oxide
20mg only-FD&C Blue 2
40mg only-D&C Yellow 10
FD&C Blue 2

Applicant:
Active: Lovastatin 10 mg, 20 mg, or 40 mg
Inactive: Lactose monohydrate
Pregelatinized Starch
Microcrystalline cellulose
Butylated Hydroxyanisole (preservative)
Magnesium stearate
10mg only-FD&C Yellow #6
20mg only-FD&C Blue #1
40mg only-

See Vol. 1.14, page 5854.

9. Storage/Dispensing

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

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

See Vol. 1.1, page 53.

Date of Review: January 12, 1999
Date of Submission: December 31, 1998

Reviewer: /S/ **Date:** 4/14/99

Team Leader: **Date:**

/S/ 4/15/1999

cc:

ANDA: 75-557
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)
V:\FIRMSNZ\TEVA\LTRS&REV\75551na1.1
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-551

CORRESPONDENCE

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

ORIG AMENDMENT
AM

September 18, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT

ANDA #75-551
LOVASTATIN TABLETS USP, 10 mg, 20 mg and 40 mg
90 DAY AMENDMENT- FINAL APPROVAL REQUESTED

Dear Mr. Buehler:

We herewith submit an amendment to the above-referenced tentatively approved abbreviated new drug application in accord with the Agency's instructions in a July 18, 2001 tentative approval letter. Please note that TEVA anticipates receipt of final approval on December 15, 2001 which is the date of expiration of pediatric exclusivity associated with U.S. Patent 4,231,938. In addition, please note that to the best of our knowledge, there is no other patent or exclusivity protection associated with the reference listed drug.

Please note that the following documents have been revised since they were last submitted to the Agency in ANDA #75-551 or amendments to the file:

Chemistry, Manufacturing and Controls:

[redacted]

CENTER FOR DRUG
SEP 19 2001
OGD
EVALUATION AND RESEARCH

/S/ 9-21

No other changes have been implemented with respect to this product since the submission of TEVA's original 90-day amendment on March 23, 2001.

This information is submitted for your review and final approval of ANDA #75-551. If you have any questions or comments regarding this submission, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

ANDA 75-551

JUL - 3 2001

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
PO Box 1090
North Wales, PA 19454

Sent by Facsimile and U.S. Mail

Dear Mr. Erickson:

This is in reference to your abbreviated new drug application dated December 31, 1998, 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 made to our approval letter dated June 15, 2001. Pursuant to the enclosed court order dated June 22, 2001, the Agency's decision to deny pediatric exclusivity for lovastatin has been vacated and remanded back to the Agency for further consideration.

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 pediatric exclusivity is denied and you are free to market, or that pediatric exclusivity is granted and you may not market until the pediatric exclusivity expires. 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/

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

7/3/01

Enclosure: Court Order dated June 22, 2001

ANDA 75-551

JUN 18 2001

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
PO Box 1090
North Wales, PA 19454

Sent by Facsimile and U.S. Mail

Dear Mr. Erickson:

This is in reference to your abbreviated new drug application dated December 31, 1998, 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 made to our approval letter dated June 15, 2001. Pursuant to the enclosed court order dated June 16, 2001, the approval of your application has been stayed.

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

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

March 23, 2001

N/A c

ORIG AMENDMENT

MINOR AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #75-551
LOVASTATIN TABLETS USP, 10 mg, 20 mg and 40 mg
90 DAY AMENDMENT

Dear Mr. Buehler:

We herewith submit an amendment to the above-referenced tentatively approved abbreviated new drug application in accord with the Agency's instructions in a September 30, 1999 tentative approval letter. Please note that TEVA anticipates receipt of final approval on June 15, 2001 which is the date of expiration of U.S. Patent 4,231,938 as listed for the reference listed drug.

Please note that the following documents have been revised since they were last submitted to the Agency in ANDA #75-551 or amendments to the file:

Chemistry, Manufacturing and Controls:

1. [redacted]

2. [redacted]

3. [redacted]

4. [redacted]

5. [redacted]

Labeling:

1. **Container Labels**: Please find enclosed in **Attachment 6** twelve copies of final print container labels for the package sizes proposed in TEVA's November 20, 2000 Unsolicited Amendment, namely Lovastatin Tablets USP, 10 mg (bottles of 60 and 1000) and Lovastatin Tablets USP, 20 mg (bottles of 60). Please note that final print container labels for all other package sizes were submitted to the Agency in a 7/29/99 facsimile amendment and were noted to be satisfactory in an 8/12/99 review letter from the Division of Labeling and Program Support.

2. **Package insert labeling** has been revised in accord with a commitment TEVA made in an August 30, 1999 amendment to omit wording from the labeling with respect to the exclusivity I-250 (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). Twelve copies of final print insert labeling are provided in **Attachment 7**. A side-by-side comparison of this version as compared to that last submitted to the Agency is provided in **Attachment 8** to aid in review.

This information is submitted for your review and final approval of ANDA #75-551. If you have any questions or comments regarding this submission, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson

PE/jbp
Enclosures

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 721 9669

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 256 7855

September 22, 1999

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

ANDA #75-551
LOVASTATIN TABLETS USP, 10 mg, 20 mg and 40 mg
TELEPHONE AMENDMENT

Dear Mr. Sporn:

We submit herewith an amendment to the above referenced pending abbreviated new drug application in accord with a telephone conversation with Mr. Bob West of the Office of Generic Drugs (OGD) on September 22, 1999. Specifically, we hereby withdraw the following _____ which was proposed in the original ANDA:

_____

_____

_____

In addition, we note that FDA inspectors are currently at our Sellersville, PA facility conducting a pre-approval inspection. The inspection is expected to be completed today, September 22, 1999. The district inspectors have indicated they will have a recommendation prepared by the end of this week.

Finally, at the request of Mr. West, please find attached a copy of an August 30, 1999 correspondence to your office which amended ANDA # 75-551 to include a certification for exclusivity I-250 and provided commitment that TEVA Pharmaceuticals USA shall exclude this indication from our insert labeling until the expiration of this exclusivity on March 11, 2002.

This information is submitted for your continued review and approval of ANDA #75-551. If you have any questions or comments regarding this submission, please do not hesitate to contact me at (215) 256-8400 ext. 5249 or via facsimile at (215) 256-8105.

Sincerely,

Deborah A. Jaskot/RS

DAJ/jpb
Enclosures

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 721 9669

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 256 7855

August 31, 1999

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

ORIG AMENDMENT

FA

ANDA #75-551
LOVASTATIN TABLETS USP, 10 mg, 20 mg and 40 mg
TELEPHONE AMENDMENT

Dear Mr. Sporn:

We submit herewith an amendment to the above referenced pending abbreviated new drug application in accord with a telephone conversation with Mr. Mike Smela and Mr. Ken Furnkranz of the Office of Generic Drugs (OGD) on August 25, 1999. Specifically, we hereby commit to further tighten the specification for Total Impurities for stability purposes to NMT ——— Please note that the release specification for Total Impurities was previously tightened to — and will remain at that limit.

In addition, at OGD's insistence, we have revised our ——————— acceptance criteria from a two-tiered specification to that of only one tier. The new specification is ——————— with an RSD of NMT —. While we have objected to this same request previously in the course of review of this ANDA, we have now conceded to make the revision solely to avoid delay of the review process of this application.

In support of these changes, please find enclosed revised control documents (a finished product procedure manual and stability protocols) noting these changed specifications.

This information is submitted for your continued review and approval of ANDA #75-551. If you have any questions or comments regarding this submission, please do not hesitate to contact me at (215) 256-8400 ext. 5249 or via facsimile at (215) 256-8105.

Sincerely,

Deborah A. Jaskot

DAJ/jpb
Enclosures

TEVA

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 721 9669

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 256 7855

August 30, 1999

NEW CORRESP
Nc

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**UNSOLICITED AMENDMENT-
EXCLUSIVITY CERTIFICATION
REVISION**

ANDA #75-551
LOVASTATIN TABLETS USP, 10 mg, 20 mg and 40 mg
UNSOLICITED AMENDMENT- EXCLUSIVITY CERTIFICATION REVISION

Dear Mr. Sporn:

We submit herewith an amendment to the above referenced abbreviated new drug application in response to a newly listed exclusivity, I-250, for the reference listed drug Mevacor Tablets in the Approved Drug Products With Therapeutic Equivalence Evaluations, Nineteenth Edition, Supplement 1. Please find enclosed a revised exclusivity statement noting this new exclusivity as well as our commitment to exclude this indication from our insert labeling until the expiration of the exclusivity on March 11, 2002.

This information is submitted for your continued review and approval of ANDA #75-551. If you have any questions or comments regarding this submission, please do not hesitate to contact me at (215) 256-8400 ext. 5249 or via facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot

DAJ/jpb
Enclosures

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 721 9669

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 256 7855

August 25, 1999

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FACSIMILE AMENDMENT

NDA ORIG AMENDMENT
N/A

ANDA #75-551
LOVASTATIN TABLETS USP, 10 mg, 20 mg and 40 mg
FACSIMILE AMENDMENT- LABELING REVISION (RESPONSE TO AUGUST 12, 1999 REVIEW LETTER)

Dear Mr. Sporn:

We submit herewith a facsimile amendment to the above referenced abbreviated new drug application in response to the review letter dated August 12, 1999 from the Division of Labeling and Program Support. All labeling deficiencies have been addressed in the updated draft insert labeling as provided herein. In addition, we have also included a comparison of the current proposed labeling versus our last submitted labeling annotating all differences. A copy of the review letter is provided for ease of review. Specifically, the following revisions were made:

- The statement "Rx only" was added to the insert labeling.
- Under Warnings (Reducing the Risk of Myopathy), the first and third sentences of number one, and the first and second sentences of number two have been bolded. In addition, the first part of the first sentence of paragraph three of number two has been bolded as directed.
- The revision date of this document was revised throughout as appropriate.

As patent protection for the reference listed drug does not expire until June 15, 2001, insert labeling is provided herein in draft form. We note and acknowledge that it may be necessary to further revise insert labeling subsequent to approved changes for the reference listed drug. Final printed labeling therefore will be provided to the Agency at least sixty days prior to full approval of this application.

In addition, we note and acknowledge that all container deficiencies have been addressed and that final print container labels that were last provided were found satisfactory.

This information is submitted for your continued review and approval of ANDA # 75-551. If you have any questions or comments regarding this submission, please do not hesitate to contact me at (215) 256-8400 ext. 5249 or via facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot

DAJ/jpb
Enclosures

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 721 9669

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 256 7855

July 29, 1999

NEW CORRESP
NC to FAX

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FACSIMILE AMENDMENT

ANDA #75-551
LOVASTATIN TABLETS USP, 10 mg, 20 mg and 40 mg
FACSIMILE AMENDMENT - RESPONSE TO REVIEW LETTER DATED JUNE 29, 1999

Dear Mr. Sporn:

We herewith submit a facsimile amendment to the above referenced abbreviated new drug application in response to the review letter from the Office of Generic Drugs (OGD) dated June 29, 1999. Our response is presented in the order in which the deficiencies were provided.

A. ***Chemistry Deficiencies***

1. [redacted]

2. [redacted]

AUG 02 1999

a. [redacted]

Redacted 3

pages of trade secret and/or

confidential

commercial

information

General Impurities Assay:

	Release	Stability
Individual Impurities	NMT —	NMT —
—	NMT —	NMT —
—	NMT —	NMT —
Total Impurities	NMT —	NMT —

Release: — of the formulated amount — mg/tablet)

B. ***In addition to the above comments, we acknowledge the following***:

1. We acknowledge that the Division of Bioequivalence has completed its review of our bioequivalence information and has no further questions at this time. However, we will assist the Division of Bioequivalence as necessary should any questions arise after their review of the entire application.

2. We acknowledge that satisfactory cGMP compliance evaluations are required for the firms referenced herein. Please refer to Attachment 1 for certifications of such compliance.

3. As the 60's package size was withdrawn in our 2/5/99 Amendment, reference to this package size has been deleted from insert labeling.

4. All stability data generated since our last submission has been provided in Attachments 5 and 6.

5. We acknowledge the labeling deficiencies noted and respond to each of them below in Item D.

C. ***Bioequivalence Comments***

Dissolution testing as currently proposed is incorporated into our stability and quality control programs as specified in the USP.

D. ***Labeling Deficiencies***

2. Container

As noted, the 60 count size for the 10 mg product was withdrawn from our ANDA in an amendment submitted to the Office of Generic Drugs on February 5, 1999. All reference to this package has been deleted from container labels and insert labeling. In addition, we originally proposed two different package configurations for the 100 count package for the 40 mg strength: a 60 cc bottle with a child-resistant cap, and a 100 cc bottle with a [redacted]. We intend to commercially market only the 100 cc bottle with [redacted] caps, therefore container labels are provided for this 40 mg strength 100 count bottle only.

a. We note that the Office of Generic Drugs does not normally approve bulk container labels. However, these container labels are of the same format and meet the same requirements as the other package sizes submitted.

b. Comments made in 2 (b) and 2 (c) are hereby acknowledged. Final printed container labels are provided as Attachment 7.

3. Insert

a. We note that the Office of Generic Drugs does not normally approve bulk container labels. However, we intend to commercially market in bulk size containers and therefore reflect such package sizes in our insert labeling.

b. Insert labeling has been revised to reflect the most recently approved labeling for the reference listed drug which was approved March 1, 1999. Draft insert labeling and a side by side comparison of proposed labeling versus that submitted in the original ANDA are provided in Attachment 8.

This information is submitted for your continued review and approval of ANDA #75-551. If you have any questions or comments regarding this submission, please do not hesitate to contact me at (215) 256-8400 ext. 5249 or via facsimile at (215) 256-8105.

Sincerely,

Deborah A. Jarchat

DAJ/jpb
Enclosures

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 721-9669

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 256-7855

March 24, 1999

NDA ORIG AMENDMENT
N/AB

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Metro Park North II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

ANDA 75-551
LOVASTATIN TABLETS USP, 10 mg, 20 mg, AND 40 mg
TELEPHONE AMENDMENT

Dear Mr. Sporn:

In response to a request from Ms. Elaine Hu of the Division of Bioequivalence, we herein provide a table which delineates the maximum storage times experienced by human plasma samples. It is shown in the attached table that the stability data generated are ample to establish the stability of both lovastatin and β-hydroxylovastatin in human serum for at least the maximum storage time.

This information is submitted for the continued review of this ANDA.

Sincerely,

Deborah Jaskot

DJ
Enclosure

RECEIVED
MAR 25 1999
GENERIC DRUGS

TEVA

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 721 9669

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 256 7855

NC

NEW CORRESP

February 5, 1999

NEW CORRESPONDENCE

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-551
LOVASTATIN TABLETS USP, 10 mg, 20 mg, and 40 mg
NEW CORRESPONDENCE - RESPONSE TO TELEPHONE CONTACT

Dear Mr. Sporn:

In response to a telephone conversation with Harvey Greenberg, of your office, we request the withdrawal of all references to the 60 count size of the 10 mg dose strength in the above referenced application. In support of this change we have attached a revised finished product stability protocol for the 10 mg dose strength. We also commit to revise our product labeling in accord with this change at the time of your first labeling revision request.

If you should have any further questions or require any further documentation, please do not hesitate to contact me at (215) 256-8400 extension 5249 or via facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot/PC

DAJ/asg
Enclosures

RECEIVED
FEB 09 (99)
GENERIC DRUGS

ANDA 75-551

Teva Pharmaceuticals USA
Attention: Deborah A. Jaskot
1510 Delph Drive
Kulpsville, PA 19443

FEB 9 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 made to the telephone conversation dated February 4, and your correspondence dated February 5, 1999.

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

DATE OF APPLICATION: December 31, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 31, 1998

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

Please identify any communications concerning this application with the ANDA 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

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 721-9669

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 256-7855

December 31, 1998

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIGINAL ABBREVIATED NEW DRUG APPLICATION
LOVASTATIN TABLETS USP, 10 mg, 20 mg, and 40 mg

Dear Mr. Sporn:

We submit herewith an abbreviated new drug application for the drug product Lovastatin Tablets USP, 10 mg, 20 mg, and 40 mg.

Enclosed are archival and review copies assembled in accord with Office of Genreic Drugs April 1997 Guidance for Industry: Organization of an Abbreviated New Drug Application and an Abbreviated Antibiotic Application. These copies are presented in a total of 33 volumes; 16 for the archival copy and 17 for the review copy.

The application contains a full report of two in vivo bioequivalence studies comparing Lovastatin Tablets USP, 40 mg manufactured by TEVA Pharmaceuticals USA, to the reference listed drug, MEVACOR® Tablets, 40 mg under both fasting and post-prandial conditions.

Please note, as a result of the change in our corporate name from LEMMON Company to TEVA Pharmaceuticals USA, some of the documents contained herein may refer to our previous corporate name. This change does not affect any of the systems, facilities, or controls presented in this application.

If you should have any questions regarding this submission or require any further documentation, please do not hesitate to contact me at (215) 256-8400 extension 5249 or via facsimile at (215) 256-8105.

We look forward to your review and comment.

Sincerely,

Deborah Jaskot RPE

DAJ/ars
Enclosures