CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21-316/S-006

Trade Name: Altocor Extended Release Tablets

Generic Name: lovastatin

Sponsor: Andrx Laboratories, Inc.

Approval Date: September 24, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-316/S-006

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-316/S-006

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-316/S-006

Andrx Laboratories, Inc.
Attention: Nicholas J. Farina, Ph.D.
Vice President, Regulatory Affairs
401 Hackensack Avenue, 9th Floor
Hackensack, NJ 07601

Dear Dr. Farina:

Please refer to your supplemental new drug application dated December 23, 2002, received December 24, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Altocor (lovastatin extended release) Tablets, 10 mg, 20mg, 40 mg, and 60 mg.

We acknowledge receipt of your submission dated July 29, 2003. Your submission of July 29, 2003, constituted a complete response to our action letter dated June 18, 2003.

This supplemental new drug application provides for revisions to:
1. CLINICAL PHARMACOLOGY/Pharacokinetics/Metabolism;
2. WARNINGS/Myopathy/Rhapdomyolysis;
3. PRECAUTIONS
4. ADVERSE REACTIONS
5. DOSAGE AND ADMINISTRATION

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

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted July 29, 2003).

Please submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA's.* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-316/S-006." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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

If you have any questions, call Valerie Jimenez, Regulatory Project Manager, at (301) 827-9090.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation

Enclosure

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

/s/

David Orloff
9/24/03 04:59:03 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-316/S-006

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-316/S-006

Andrx Laboratories, Inc.
Attention: Nicholas Farina, Ph.D.
Vice President, Regulatory Affairs
401 Hackensack Avenue
Hackensack, NJ 07601

Dear Dr. Farina:

Please refer to your new drug application (NDA) dated December 23, 2003, received December 24, 2003, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Altocor (lovastatin) Extended Release Tablets.

We completed our review of this application, as amended, and it is approvable. Before this application may be approved, however, you must submit revised draft printed labeling such that the statement pertaining to monitoring of liver function tests reads as follows:

> "It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation of dose, periodically thereafter (e.g., semiannually)".

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, call Valerie Jimenez, Regulatory Project Manager, at (301) 827-9090.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products-HFD 510
Office of Drug Evaluation II
Center for Drug Evaluation

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

/s/

David Orloff
6/18/03 02:17:48 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-316/S-006

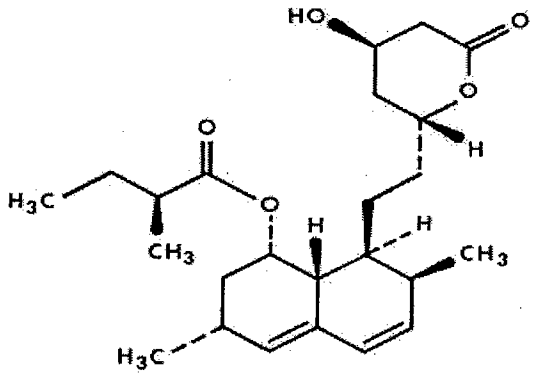
APPROVED LABELING

ALTOCOR™ EXTENDED-RELEASE TABLETS
(LOVASTATIN)

DESCRIPTION

ALTOCOR™ (Lovastatin) Extended-Release Tablets contain 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 inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate limiting step in the biosynthesis of cholesterol.

Lovastatin is [1 *S* -[1α(*R**),3α,7β,8β(2 *S**,4 *S**),8aβ]]-1,2,3, 7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2 *H* -pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate. The empirical formula of lovastatin is $C_{24}H_{36}O_5$ and its molecular weight is 404.55. Its structural formula is:



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

ALTOCOR™ Extended-Release Tablets are designed for once-a-day oral administration and deliver 10 mg, 20 mg, 40 mg, or 60 mg of lovastatin. In addition to the active ingredient lovastatin, each tablet contains the following inactive ingredients: acetyltributyl citrate; butylated hydroxyanisole; candellila wax; cellulose acetate; confectioner's sugar (contains corn starch); F D & C yellow # 6; glyceryl monostearate; hydroxypropyl methylcellulose; hypromellose phthalate; lactose; methacrylic acid copolymer, type B; polyethylene glycols (PEG 400, PEG 8000); polyethylene oxides; polysorbate 80; propylene glycol; silicon dioxide; sodium chloride; sodium lauryl sulfate; synthetic black iron oxide; red iron oxide; talc; titanium dioxide and triacetin.

CLINICAL PHARMACOLOGY

Mechanism of Action

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

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) levels 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 levels in the lower end of this range.

ALTOCOR™ has been shown to reduce LDL-C, and Total-C. Across all doses studied, treatment with ALTOCOR™ has been shown to result in variable reductions in triglycerides (TG), and variable increases in HDL-C (see Table III under *Clinical Studies*).

Lovastatin immediate-release tablets have 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 immediate-release 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 (Apo B) also falls substantially during treatment with lovastatin immediate-release. Since each LDL particle contains one molecule of Apo B, and since little Apo B is found in other lipoproteins, this strongly suggests that lovastatin immediate-release does not merely cause cholesterol to be lost from LDL, but also reduces the concentration of circulating LDL particles. In addition, lovastatin immediate-release can produce increases of variable magnitude in HDL-C, and modestly reduces VLDL-C and plasma TG (see Table IV under *Clinical Studies*). The independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined. The effects of lovastatin immediate-release on lipoprotein (a) [Lp(a)], fibrinogen, and certain other independent biochemical risk markers for coronary heart disease are unknown.

Lovastatin, as well as some of its metabolites, are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance (see **DOSAGE AND ADMINISTRATION**).

Pharmacokinetics and Drug Metabolism

Absorption

ALTOCOR™

The appearance of lovastatin in plasma from an ALTOCOR™ Extended-Release Tablet is slower and more prolonged compared to the lovastatin immediate-release formulation.

A pharmacokinetic study carried out with ALTOCOR™ involved measurement of the systemic concentrations of lovastatin (pro-drug), lovastatin acid (active-drug) and total and active inhibitors of HMG-CoA reductase. The pharmacokinetic parameters in 12 hypercholesterolemic subjects at steady state, after 28 days of treatment, comparing ALTOCOR™ 40 mg to lovastatin immediate-release 40 mg, are summarized in **Table I**.

Table I
ALTOCOR™ vs Lovastatin Immediate-Release (IR)
(Steady-State Pharmacokinetic Parameters at Day 28)

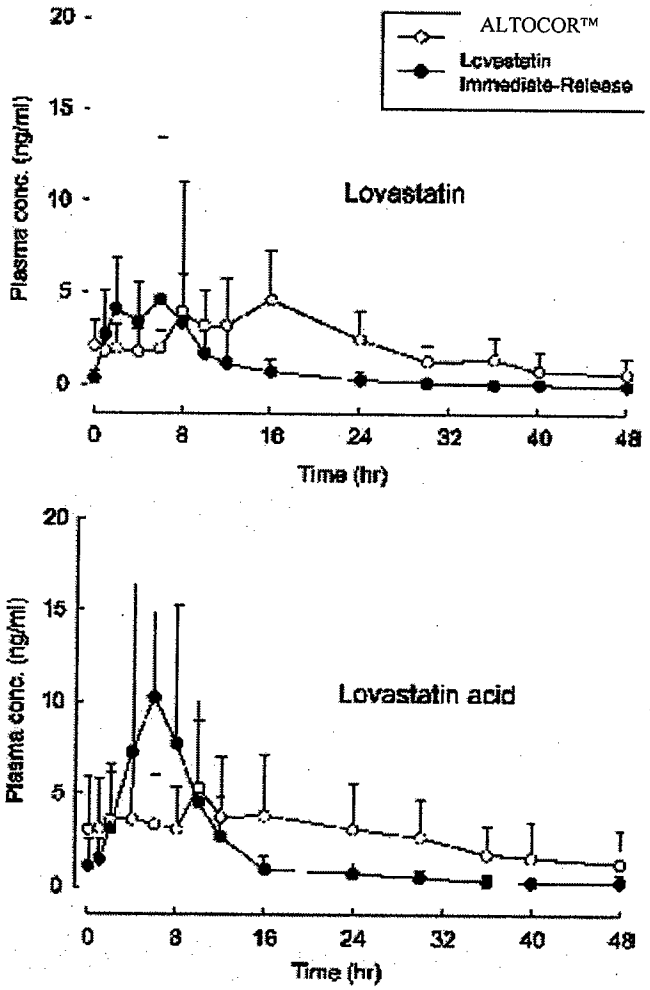
Drug	C_{max} (ng/mL)				C_{min} (ng/mL)				T_{max} (h)		$AUC_{0\text{-}24hr}$ (ng·h/mL)			
	L	LA	TI	AI	L	LA	TI	AI	L	LA	L	LA	TI	AI
ALTOCOR™ 40 mg*	5.5	5.8	17.3	13.4	2.6	3.1	9.1	4.3	14.2	11.8	77	87	263	171
Lovastatin IR 40 mg**	7.8	11.9	36.2	26.6	0.4	0.7	2.4	2.1	3.3	5.3	45	83	252	186

L=lovastatin, LA=lovastatin acid, TI=total inhibitors of HMG-CoA reductase, AI=active inhibitors of HMG-CoA reductase, C_{max}=highest observed plasma concentration, C_{min}=trough concentration at t=24 hours after dosing, T_{max}=time at which the C_{max} occurred, $AUC_{0\text{-}24hr}$=area under the plasma concentration-time curve from time 0 to 24 hr after dosing, calculated by the linear trapezoidal rule.
* Administered at bedtime
** Administered with the evening meal.

The mean plasma concentration-time profiles of lovastatin and lovastatin acid in patients after multiple doses of ALTOCOR™ or lovastatin immediate-release at day 28 are shown in **Figure 1**.

Figure 1

Mean (SD) plasma concentration-time profiles of lovastatin and lovastatin acid in hypercholesterolemic patients (n=12) after 28 days of administration of ALTOCOR™ or lovastatin immediate release



The extended-release properties of ALTOCOR™ are characterized by a prolonged absorptive phase, which results in a longer T_{max} and lower C_{max} for lovastatin (prodrug) and its major metabolite, lovastatin acid, compared to lovastatin immediate-release.

The bioavailability of lovastatin (pro-drug) as measured by the $AUC_{0\text{-}24hr}$ was greater for ALTOCOR™ compared to lovastatin immediate-release (as measured by a chemical assay), while the bioavailability of total and active inhibitors of HMG-CoA reductase were equivalent to lovastatin immediate-release (as measured by an enzymatic assay).

With once-a-day dosing, mean values of AUCs of active and total inhibitors at steady state were about 1.8 -1.9 times those following a single dose. Accumulation ratio of lovastatin exposure was 1.5 after multiple daily doses of ALTOCOR™ compared to that of a single dose measured using a chemical assay.

ALTOCOR™ appears to have dose linearity for doses from 10 mg up to 60 mg per day.

When ALTOCOR™ was given after a meal, plasma concentrations of lovastatin and lovastatin acid were about 0.5 - 0.6 times those found when ALTOCOR™ was administered in the fasting state, indicating that food decreases the bioavailability of ALTOCOR™. There was an association between the bioavailability of ALTOCOR™ and dosing after mealtimes. Bioavailability was lowered under the following conditions, (from higher bioavailability to lower bioavailability) in the following order: under overnight fasting conditions, before bedtime, with dinner, and with a high fat breakfast. In a multicenter, randomized, parallel group study, patients were administered 40 mg of ALTOCOR™ at three different times; before breakfast, after dinner and at bedtime. Although there was no statistical difference in the extent of lipid change between the three groups, there was a numerically greater reduction in LDL-C and TG and an increase in HDL-C when ALTOCOR™ was administered at bedtime. Results of this study are displayed in **Table II**.

Table II
ALTOCOR™ 40 mg
(Least Squares Mean Percent Changes from Baseline to Endpoint at 4 weeks of treatment*)

	LDL-C	HDL-C	TOTAL-C	TG
Before Breakfast	-32.0%	8.4%	-22.2%	-10.2%
After Dinner	-34.1%	7.4%	-23.6%	-11.2%
Before Bedtime	-36.9%	11.1%	-25.5%	-19.7%

N=22 for the Before Breakfast group, N=23 for the After Dinner group, and N=23 for the Before Bedtime group.
*All changes from baseline are statistically significant.

At steady state in humans, the bioavailability of lovastatin, following the administration of ALTOCOR™, was 190% compared to lovastatin immediate-release.

Lovastatin Immediate-Release

Absorption of lovastatin, estimated relative to an intravenous reference dose in each of four animal species tested, averaged about 30% of an oral dose. 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. 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.

Distribution

Lovastatin

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.

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.

Metabolism

Metabolism studies with ALTOCOR™ have not been conducted.

Lovastatin

Lovastatin is a lactone that 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.

The major active metabolites present in human plasma are the β-hydroxyacid of lovastatin, its 6'-hydroxy derivative, and two additional metabolites.
The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Potent inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy (see **WARNINGS**, *Myopathy/Rhabdomyolysis* and **PRECAUTIONS**, *Drug Interactions*).

Lovastatin is a substrate for 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,[1] 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 mean increases in the concentration of lovastatin and its beta-hydroxyacid metabolite (as measured by the area under the concentration-time curve) of 15-fold and 5-fold respectively (as measured using a chemical assay – liquid chromatography/tandem mass spectrometry). 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 a validated enzyme inhibition assay different from that used in the first study, 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) 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.

Excretion

ALTOCOR™

In a single-dose study with ALTOCOR™, the amounts of lovastatin and lovastatin acid excreted in the urine were below the lower limit of quantitation of the assay (1.0 ng/mL), indicating that negligible excretion of ALTOCOR™ occurs through the kidney.

Lovastatin

Lovastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile.

Special Populations

Geriatric

Lovastatin Immediate-Release

In a study with lovastatin immediate-release which included 16 elderly patients between 70-78 years of age who received lovastatin immediate-release 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*)

Pediatric

Pharmacokinetic data in the pediatric population are not available.

Gender

In a single dose pharmacokinetic study with ALTOCOR™, there were no statistically significant differences in pharmacokinetic parameters between men (n=12) and women (n=10), although exposure tended to be higher in men than women.

In clinical studies with ALTOCOR™, there was no clinically significant difference in LDL-C reduction between men and women.

Renal Insufficiency

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.

Hemodialysis

The effect of hemodialysis on plasma levels of lovastatin and its metabolites have not been studied.

Hepatic Insufficiency

No pharmacokinetic studies with ALTOCOR™ have been conducted in patients with hepatic insufficiency.

Clinical Studies

ALTOCOR™

ALTOCOR™ has been shown to reduce Total-C, LDL-C, and TG and increase HDL-C in patients with hypercholesterolemia. Near maximal response was observed after four weeks of treatment and the response was maintained with continuation of therapy for up to 6 months.

In a 12-week, multicenter, placebo-controlled, double-blind, dose-response study in adult men and women 21 to 70 years of age with primary hypercholesterolemia, once daily administration of ALTOCOR™ 10 to 60 mg in the evening was compared to placebo. ALTOCOR™ produced dose related reductions in LDL-C and Total-C. ALTOCOR™ produced mean reductions in TG across all doses that varied from approximately 10% to 25%. ALTOCOR™ produced mean increases in HDL-C across all doses that varied from approximately 9% to 13%.

The lipid changes with ALTOCOR™ treatment in this study, from baseline to endpoint, are displayed in **Table III**.

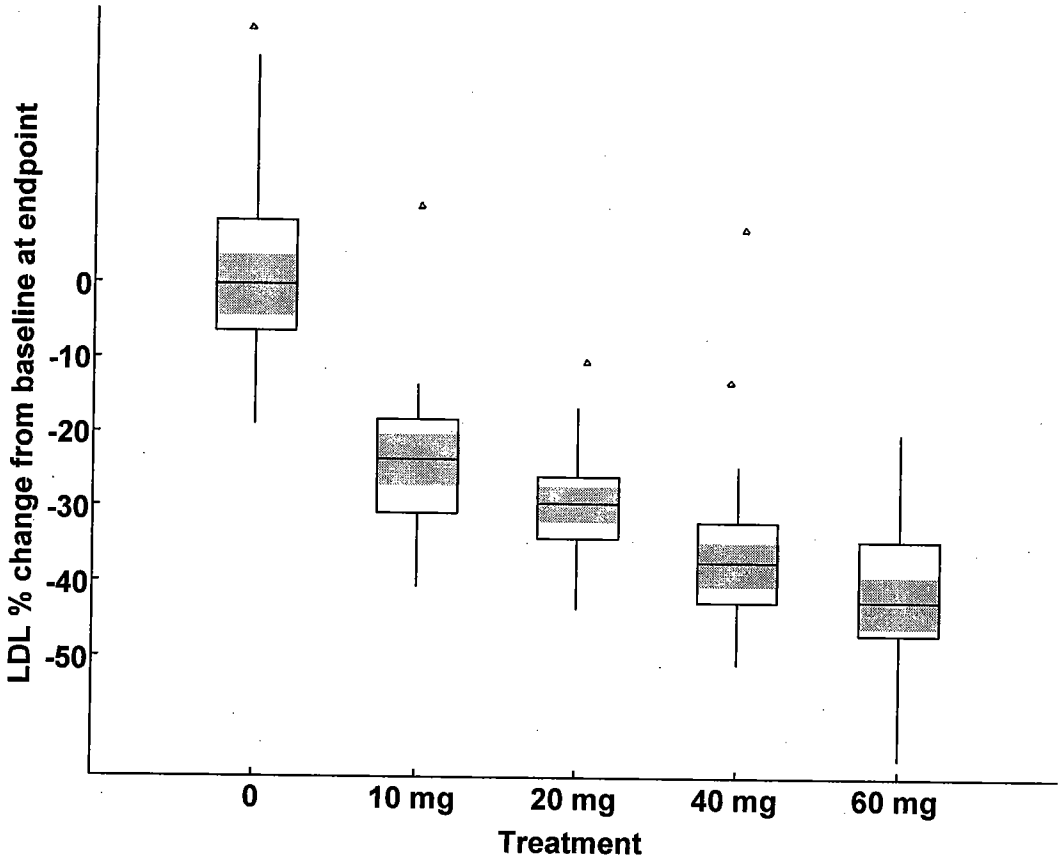
Table III
ALTOCOR™ vs. Placebo
(Mean Percent Change from Baseline After 12 Weeks)*

Treatment	N	LDL-C	HDL-C	TOTAL-C	TG
Placebo	34	1.3	5.6	3.4	8.7
ALTOCOR™ 10 mg	33	-23.8	9.4	-17.9	-17.3
ALTOCOR™ 20 mg	34**	-29.6	12.0	-20.9	-13.0
ALTOCOR™ 40 mg	33	-35.8	13.1	-25.4	-9.9
ALTOCOR™ 60 mg	35	-40.8	11.6	-29.2	-25.1

N= the number of patients with values at both baseline and endpoint.
*Except for the HDL-C elevation with ALTOCOR™ 10 mg, all lipid changes with ALTOCOR™ were statistically significant compared to placebo..
**For LDL-C, 33 patients had values at baseline and endpoint.

The range of LDL-C responses is represented graphically in the following figure (**Figure 2**):

Figure 2
ALTOCOR™ vs Placebo
LDL-C Percent Change from Baseline After 12 Weeks



The distribution of LDL-C responses is represented graphically by the boxplots in **Figure 2**. The bottom line of the box represents the 25th percentile and the top line, the 75th percentile. The horizontal line in the box represents the median and the gray area is the 95% confidence interval for the median. The range of responses is depicted by the tails and outliers.

ALTOCOR™ Long-Term Study

A total of 365 patients were enrolled in an extension study in which all patients were administered ALTOCOR™ 40 mg or 60 mg once daily for up to 6 months of treatment. The lipid-altering effects of ALTOCOR™ were comparable to what was observed in the dose-response study, and were maintained for up to 6 months of treatment.

Special Populations
In clinical studies with ALTOCOR™, there were no statistically significant differences in LDL-C reduction in an older population (≥65 years old), compared to a younger population (<65 years old). There were also no statistically significant differences in LDL-C reduction between male and female patients.

Lovastatin Immediate-Release

Lovastatin immediate-release has been shown to be 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.

Lovastatin immediate-release was studied in controlled trials in hypercholesterolemic patients with well-controlled non-insulin dependent diabetes mellitus with normal renal function. The effect of lovastatin immediate-release on lipids and lipoproteins and the safety profile of lovastatin immediate-release were similar to that demonstrated in studies in nondiabetics. Lovastatin immediate-release 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 immediate-release 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 (see **Table IV**) observed in lovastatin immediate-release-treated patients were dose-related and significantly different from placebo ($p \leq 0.001$). These results were sustained throughout the study.

TABLE IV
Lovastatin Immediate-Release (IR) 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 IR							
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

Lovastatin Immediate-Release

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

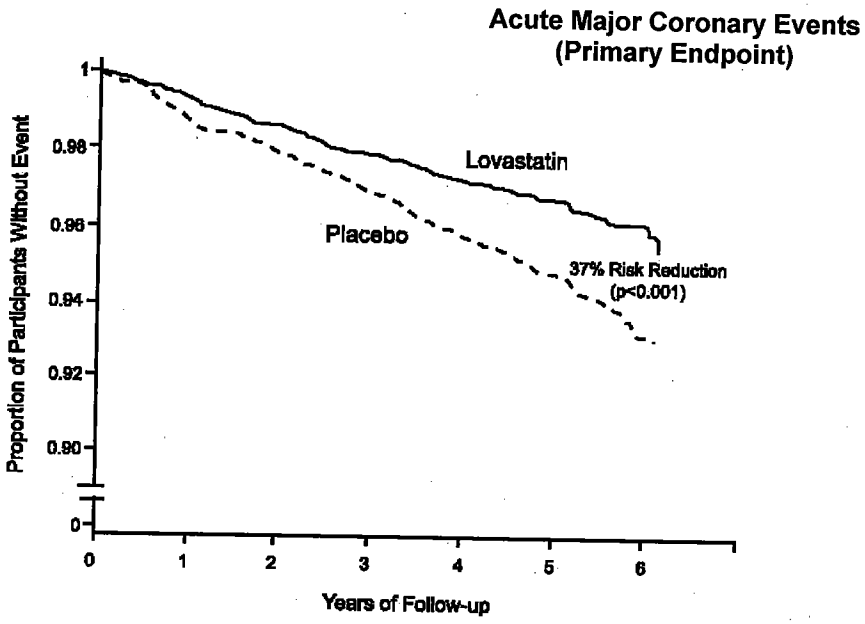
The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), a double-blind, randomized, placebo-controlled, primary prevention study, demonstrated that treatment with lovastatin immediate-release decreased the rate of acute major coronary events (composite endpoint of myocardial infarction,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

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

Lovastatin immediate-release reduced the risk of a first acute major coronary event, the primary efficacy endpoint, by 37% (lovastatin immediate-release 3.5%, placebo 5.5%; p<0.001; **Figure 3**). A first acute major coronary event was defined as myocardial infarction (54 participants on lovastatin immediate-release, 94 on placebo) or unstable angina (54 vs. 80) or sudden cardiac death (8 vs. 9). Furthermore, among the secondary endpoints, lovastatin immediate-release reduced the risk of unstable angina by 32% (1.8% vs. 2.6%; p=0.023), of myocardial infarction by 40% (1.7% vs. 2.9%; p=0.002), and of undergoing coronary revascularization procedures (e.g., coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 33% (3.2% vs. 4.8%; p=0.001). Trends in risk reduction associated with treatment with lovastatin immediate-release were consistent across men and women, smokers and non-smokers, hypertensives and non-hypertensives, and older and younger participants. Participants with ≥2 risk factors had risk reductions (RR) in both acute

major coronary events (RR 43%) and coronary revascularization procedures (RR 37%). Because there were too few events among those participants with age as their only risk factor in this study, the effect of lovastatin immediate-release on outcomes could not be adequately assessed in this subgroup.

Figure 3



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 this 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 mg - 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.

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 immediate-release. During these trials the appearance of new opacities was noted in both the lovastatin immediate-release 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 immediate-release on the human lens demonstrated that there were no clinically or statistically significant differences between the lovastatin immediate-release 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 ALTOCOR™ (Lovastatin) Extended-Release Tablets should be a component of multiple risk factor intervention in those individuals with dyslipidemia who are at risk for atherosclerotic

vascular disease. ALTOCOR™ 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.

ALTOCOR™

Primary Prevention of Coronary Heart Disease

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

- MYOCARDIAL INFARCTION
- UNSTABLE ANGINA
- CORONARY REVASCULARIZATION PROCEDURES

(See CLINICAL PHARMACOLOGY, *Clinical Studies*.)

Coronary Heart Disease

ALTOCOR™ 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.

Hyperlipidemia

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

ALTOCOR™ is indicated as an adjunct to diet for the reduction of elevated Total-C, LDL-C, Apo B, and TG, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and non-familial) and mixed dyslipidemia (Fredrickson types IIa and IIb, see **Table VI**) when the response to diet restricted in saturated fat and cholesterol and to other non-pharmacological measures alone has been inadequate.

General Recommendations

Prior to initiating therapy with ALTOCOR™, 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, ALTOCOR™ is not indicated.

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

Table V
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 <100mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.
††† Almost all people with 0-1 risk factor have 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 ALTOCOR™ 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). [See **Table VI**]

Table VI
Classification of Hyperlipoproteinemias

Type	Lipoproteins Elevated	Lipid Elevations	
		Major	Minor
I (rare)	Chylomicrons	TG	↑→TC
IIa	LDL	TC	-
IIb	LDL, VLDL	TC	TG
III (rare)	IDL	TC/TG	-
IV	VLDL	TG	↑→TC
V (rare)	Chylomicrons, VLDL	TG	↑→TC

TC = total cholesterol; TG = triglycerides; LDL = low-density lipoprotein;
VLDL = very low-density lipoprotein; IDL = intermediate-density lipoprotein
↑→ = increased or no change

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 ALTOCOR™ to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, ALTOCOR™ is contraindicated during pregnancy and in nursing mothers. **ALTOCOR™ 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, ALTOCOR™ should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see **PRECAUTIONS**, *Pregnancy*).

WARNINGS

Myopathy/Rhabdomyolysis
Lovastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10X the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

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

Potent inhibitors of CYP3A4: Cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily), particularly with higher doses of lovastatin (see below; **CLINICAL PHARMACOLOGY**, *Pharmacokinetics*; PRECAUTIONS, *Drug Interactions, CYP3A4 Interactions*).

Lipid-lowering drugs that can cause myopathy when given alone: Gemfibrozil, other fibrates, or lipid-lowering doses (≥1 g/day) of niacin, particularly with higher doses of lovastatin (see below; **CLINICAL PHARMACOLOGY**, *Pharmacokinetics*; **PRECAUTIONS**, *Drug Interactions,Interactions with lipid-lowering drugs that can cause myopathy when given alone*).

Other drugs: The risk of myopathy/rhabdomyolysis is increased when either amiodarone or verapamil is used concomitantly with higher doses of a closely related member of the HMG-CoA reductase inhibitor class (see **PRECAUTIONS**, *Drug Interactions, Other drug interactions*).

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

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

2. The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with cyclosporine, gemfibrozil, other fibrates or lipid-lowering doses (≥1 g/day) of niacin. The combined use of lovastatin with fibrates or niacin should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug

combination. Addition of these drugs to lovastatin typically provides little additional reduction in LDL-C, but further reductions of TG and further increases in HDL-C may be obtained.

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

4. All patients starting therapy with lovastatin, or whose dose of lovastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Lovastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. The presence of these symptoms, and/or a CK level >10 times the ULN indicates myopathy. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved. Periodic CK determinations may be considered in patients starting therapy with lovastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

5. Many of the patients who have developed rhabdomyolysis on therapy with lovastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. Therapy with lovastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Liver Dysfunction

Persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least one year in early clinical trials (see ADVERSE REACTIONS). When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin, and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

ALTOCOR™

In controlled clinical trials (467 patients treated with ALTOCOR™ and 329 patients treated with lovastatin immediate-release) no meaningful differences in transaminase elevations between the two treatments were observed.

Lovastatin Immediate-Release

In the EXCEL study (see **CLINICAL PHARMACOLOGY**, *Clinical Studies*), the incidence of persistent increases in serum transaminases over 48 weeks was 0.1% for placebo, 0.1% at 20 mg/day, 0.9% at 40 mg/day, and 1.5% at 80 mg/day in patients on lovastatin. However, in post-marketing experience with lovastatin immediate-release, symptomatic liver disease has been reported rarely at all dosages (see **ADVERSE REACTIONS**).

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

It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation of dose, and periodically thereafter (e.g., semiannually).

Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist, withdrawal of therapy with ALTOCOR™ is recommended.

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

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

PRECAUTIONS

General

ALTOCOR™ may elevate creatine phosphokinase and transaminase levels (see **WARNINGS** and **ADVERSE REACTIONS**). This should be considered in the differential diagnosis of chest pain in a patient on therapy with ALTOCOR™.

Homozygous Familial Hypercholesterolemia

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

Information for Patients

The ALTOCOR™ Extended-Release Tablets should be swallowed whole and not chewed, crushed, or cut.

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

Drug Interactions

Drug interaction studies have not been performed with ALTOCOR™. The types, frequencies and magnitude of drug interactions that may be encountered when ALTOCOR™ is administered with other drugs may differ from the drug interactions encountered with the lovastatin immediate-release formulation. In addition, as the drug exposure with ALTOCOR™ 60 mg is greater than that with lovastatin immediate-release 80 mg (maximum recommended dose), the severity and magnitude of drug interactions that may be encountered with ALTOCOR™ 60 mg are not known. It is therefore recommended that the following precautions and recommendations for the concomitant administration of lovastatin immediate-release with other drugs be interpreted with caution, and that the monitoring of the pharmacologic effects of ALTOCOR™ and/or other concomitantly administered drugs be undertaken where appropriate.

CYP3A4 Interactions
Lovastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of lovastatin. **See WARNINGS, *Myopathy/Rhabdomyolysis*, and CLINICAL PHARMACOLOGY, *Pharmacokinetics.***
Itraconazole
Ketoconazole
Erythromycin
Clarithromycin
HIV protease inhibitors

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

Interactions with lipid-lowering drugs that can cause myopathy when given alone
The risk of myopathy is also increased by the following lipid-lowering drugs that are not potent CYP3A4 inhibitors, but which can cause myopathy when given alone.
See WARNINGS, *Myopathy/Rhabdomyolysis.*
Gemfibrozil
Other fibrates
Niacin (nicotinic acid) (≥1 g/day)

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

Coumarin Anticoagulants: In a small clinical trial in which lovastatin was administered to warfarin treated patients, no effect on prothrombin time was detected. However, another HMG-CoA reductase inhibitor has been found to produce a less than two seconds increase in prothrombin time in healthy volunteers receiving low doses of warfarin. Also, bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. It is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Antipyrine: Lovastatin had no effect on the pharmacokinetics of antipyrine or its metabolites. However, since lovastatin is metabolized by the cytochrome P450 isoform 3A4, this does not preclude an interaction with other drugs metabolized by the same isoform (see **WARNINGS**, *Myopathy/Rhabdomyolysis*).

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

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

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

Endocrine Function

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

CNS Toxicity

Lovastatin produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). Vestibulocochlear Wallerian-like degeneration and
retinal ganglion cell chromatolysis were also seen in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level (C_{max}) similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels, were seen in dogs treated with lovastatin at a dose of 180 mg/kg/day, a dose which produced plasma drug levels (C_{max}) which were about 30 times higher than the mean values in humans taking 80 mg/day.

Similar optic nerve and CNS vascular lesions have been observed with other drugs of this class. Cataracts were seen in dogs treated for 11 and 28 weeks at 180 mg/kg/day and 1 year at 60 mg/kg/day.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 21-month carcinogenic study in mice with lovastatin immediate-release, there was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in both males and females at 500 mg/kg/day. This dose produced a total plasma drug exposure 3 to 4 times that of humans given the highest recommended dose of lovastatin (drug exposure was measured as total HMG-CoA reductase inhibitory activity in extracted plasma). Tumor increases were not seen at 20 and 100 mg/kg/day, doses that produced drug exposures of 0.3 to 2 times that of humans at the 80 mg/day lovastatin immediate-release dose. A statistically significant increase in pulmonary adenomas was seen in female mice at approximately 4 times the human drug exposure. [Although mice were given 300 times the human dose (HD) on a mg/kg body weight basis, plasma levels of total inhibitory activity were only 4 times higher in mice than in humans given 80 mg of lovastatin immediate-release].

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

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

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

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose of lovastatin immediate-release. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high dose mice than in controls.

No evidence of mutagenicity was observed with lovastatin immediate-release in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation were seen in dogs starting at 20 mg/kg/day with lovastatin immediate-release. Similar findings were seen with another drug in this class. No drug-related effects on fertility were found in studies with lovastatin in rats. However, in studies with a similar drug in this class, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. No microscopic changes were observed in the testes from rats of either study. The clinical significance of these findings is unclear.

Pregnancy

Pregnancy Category X

See **CONTRAINDICATIONS**.

Safety in pregnant women has not been established. Lovastatin immediate-release has been shown to produce skeletal malformations at plasma levels 40 times the human exposure (for mouse fetus) and 80 times the human exposure (for rat fetus) based on mg/m^2 surface area (doses were 800 mg/kg/day). No

drug-induced changes were seen in either species at multiples of 8 times (rat) or 4 times (mouse) based on surface area. No evidence of malformations was noted in rabbits at exposures up to 3 times the human exposure (dose of 15 mg/kg/day, highest tolerated dose of lovastatin immediate-release).

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review[2] of approximately 100 prospectively followed pregnancies in women exposed to lovastatin immediate-release 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 ALTOCOR™ during pregnancy (see **CONTRAINDICATIONS**), treatment should be immediately discontinued as soon as pregnancy is recognized. ALTOCOR™ 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 hazard.

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 ALTOCOR™ 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 ALTOCOR™ is not recommended at this time.

Geriatric Use

ALTOCOR™

Of the 467 patients who received ALTOCOR™ in controlled clinical studies, 18% were 65 years and older. Of the 297 patients who received ALTOCOR™ in uncontrolled clinical studies, 22% were 65 years and older. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Lovastatin Immediate-Release

In pharmacokinetic studies with lovastatin immediate-release, the mean plasma level of HMG-CoA reductase inhibitory activity was shown to be approximately 45% higher in elderly patients between 70-78 years of age compared with patients between 18-30 years of age; however, clinical study

experience in the elderly indicates that dosage adjustment based on this age-related pharmacokinetic difference is not needed. In the two large clinical studies conducted with lovastatin immediate-release (EXCEL and AFCAPS/TexCAPS), 21% (3094/14850) of patients were ≥65 years of age. Lipid-lowering efficacy with lovastatin was at least as great in elderly patients compared with younger patients, and there were no overall differences in safety over the 20 to 80 mg dosage range (see **CLINICAL PHARMACOLOGY**).

ADVERSE REACTIONS

ALTOCOR™

ALTOCOR™ Clinical Studies

In clinical studies with ALTOCOR™, adverse reactions have generally been mild and transient. In controlled studies with 467 patients who received ALTOCOR™, <3% of patients were discontinued due to adverse experiences attributable to ALTOCOR™. This was similar to the discontinuation rate in the placebo and lovastatin immediate-release treatment groups. Pooled results from clinical studies with ALTOCOR™ show that the most frequently reported adverse reactions in the ALTOCOR™ group were infection, headache and accidental injury. Similar incidences of these adverse reactions were seen in the lovastatin and placebo groups. The most frequent adverse events thought to be related to ALTOCOR™ were nausea, abdominal pain, insomnia, dyspepsia, headache, asthenia, and myalgia. In controlled trials (e.g., vs. placebo and vs. lovastatin immediate-release), clinical adverse experiences reported as ≥5% in any treatment group are shown in **Table VII** below.

Table VII
Pooled Controlled Studies TESS by Body System and COSTART Term, Most Common (≥5% in Any Group)

		Treatment		
Randomized Patients, n =		**Placebo 34**	**ALTOCOR™ 467**	**MEVACOR™ 329**
Body System	**COSTART Term**			
Body as a Whole	Infection	3 (9)	52 (11)	52 (16)
	Accidental Injury	3 (9)	26 (6)	12 (4)
	Asthenia	2 (6)	12 (3)	6 (2)
	Headache	2 (6)	34 (7)	26 (8)
	Back Pain	1 (3)	23 (5)	18 (5)
	Flu Syndrome	1 (3)	24 (5)	18 (5)
	Pain	0	14 (3)	17 (5)
Digestive	Diarrhea	2 (6)	15 (3)	8 (2)
Musculoskeletal	Arthralgia	2 (6)	24 (5)	20 (6)
	Myalgia	5 (15)	14 (3)	11 (3)
Nervous	Dizziness	2 (6)	10 (2)	5 (2)
Respiratory	Sinusitis	1 (3)	17 (4)	20 (6)
Urogenital	Urinary Tract Infection	2 (6)	8 (2)	9 (3)

Lovastatin Immediate-Release

Lovastatin Immediate-Release Phase III Clinical Studies

In Phase III controlled clinical studies involving 613 patients treated with lovastatin immediate-release, 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 %. This was attributable to the noncardiac fraction of CK. Large increases in CK have sometimes been reported (see **WARNINGS**, *Myopathy/Rhabdomyolysis*).

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study

Lovastatin immediate-release 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.

Table VIII
Clinical Adverse Events Reported as Possibly, Probably or Definitely Drug-Related in ≥1% in Any Treatment Group in the EXCEL Study

	Placebo (N=1663) %	Lovastatin IR 20 mg q.p.m. (N=1642) %	Lovastatin IR 40 mg q.p.m. (N=1645) %	Lovastatin IR 20 mg b.i.d. (N=1646) %	Lovastatin IR 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% 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 immediate-release. The value for the placebo group was 2.5%.

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

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

Concomitant Therapy

In controlled clinical studies in which lovastatin immediate-release 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**, *Myopathy/Rhabdomyolysis*)

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

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

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

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 immediate-release to mice the median lethal dose observed was >15 g/m^2.

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

Until further experience is obtained, no specific treatment of overdosage with ALTOCOR™ 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 ALTOCOR™ and should continue on this diet during treatment with ALTOCOR™ (see NCEP Treatment Guidelines for details on dietary therapy).

The usual recommended starting dose is 20, 40, or 60 mg once a day given in the evening at bedtime. The recommended dosing range is 10-60 mg/day, in single doses. Doses should be individualized according to the recommended goal of therapy (see NCEP Guidelines and **CLINICAL PHARMACOLOGY**). 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.

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

Dosage in Patients Taking Cyclosporine
In patients taking cyclosporine concomitantly with ALTOCOR™ (see **WARNINGS**, *Myopathy/Rhabdomyolysis*), therapy should begin with 10 mg of ALTOCOR™ and should not exceed 20 mg/day.

Dosage in Patients Taking Amiodarone or Verapamil

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

Concomitant Lipid-Lowering Therapy

Use of ALTOCOR™ with fibrates or niacin should generally be avoided. However, if ALTOCOR™ is used in combination with gemfibrozil, other fibrates, or lipid-lowering doses (≥ 1 g/day) of niacin, the dose of ALTOCOR™ should not exceed 20 mg (see **WARNINGS**, *Myopathy/Rhabdomyolysis* and **PRECAUTIONS**, *Drug Interactions*).

Dosage in Patients with Renal Insufficiency

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

HOW SUPPLIED

ALTOCOR™ (Lovastatin) Extended-Release Tablets are supplied as round, convex shaped tablets containing 10 mg, 20 mg, 40 mg and 60 mg of lovastatin.

NDC 62022-760-30: 10 mg extended-release dark orange-colored tablets imprinted with Andrx logo and 10 on one side, bottles of 30.

NDC 62022-770-30: 20 mg extended-release orange-colored tablets imprinted with Andrx logo and 20 on one side, bottles of 30.

NDC 62022-780-30: 40 mg extended-release peach-colored tablets imprinted with Andrx logo and 40 on one side, bottles of 30.

NDC 62022-781-30: 60 mg extended-release light peach-colored tablets imprinted with Andrx logo and 60 on one side, bottles of 30.

Storage
Store at controlled room temperature 20°- 25° C (68°- 77°F) Avoid excessive heat and humidity.

Rx only

Distributed by
Andrx Laboratories, Inc.
Weston, Florida 33331

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Rev. date: 7/03 7199

References:

1. Kantola, T, et al. Clin Pharmacol Ther 1998; 63(4):397-402.
2. Manson, J.M., Freyssinges, C., Ducrocq, M.B., Stephenson, W.P., Postmarketing Surveillance of Lovastatin and Simvastatin Exposure During Pregnancy. Reproductive Toxicology. 19(6):439-446. 1996.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-316/S-006

MEDICAL REVIEW(s)

Medical Officer's Review of Labeling Supplement

NDA#:	21-316; SLR 006 (Labeling Supplement)
Drug:	Altocor (lovastatin extended-release)
Sponsor:	Andrx Labs, Inc.
Reviewer:	Anne Pariser, M.D.
Date of Submission:	23-December-2002
Review Date:	21-May-2003

Re: Labeling Supplement for Safety Revisions to Existing Altocor Label

I. Introduction and Background

A. Introduction

The sponsor (Andrx Labs, Inc.) has submitted a labeling supplement for Altocor (lovastatin extended-release): SNDA 21-316; SLR 006, dated 23-December-2002. This supplement is proposing revisions to the safety section of the label, to include:

1. The incorporation of recent changes to the Mevacor (innovator drug) package insert (PI); and
2. A reduction in the frequency of liver enzyme testing based on
   - recent clinical trials results from completed and ongoing trials with Altocor
   - post-marketing surveillance of Altocor, and
   - data from the public domain that the sponsor states has been reviewed by the FDA

Altocor has been commercially available since its approval in 26-June-2002. Altocor's safety and efficacy is described in the Altocor label. For additional background information on Altocor, please see the following recent reviews:

- Medical Officer's Review of (initial) NDA 505(b)(2) application [Pariser A, MD, Medical Officer's Review of NDA 21-261; 000, dated 09-January-2002]
- Statistical Review and Evaluation of (initial) NDA 21-316 [Mele J, MS, Statistical Review and Evaluation, dated 03-December-2001]
- Medical Officer's Review of SNDA for primary prevention of coronary heart disease (CHD) indication based on the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[1] data for Mevacor [Pariser A, MD, Medical Officer's Review of SNDA 21-316; SE1 001, dated 31-July-2002]
- Medical Officer's Review of Periodic Safety Report (Quarterly Report) for the time period 26-September-2002 to 25-December 2002 [Pariser A, MD, Medical Officer's Review of Periodic Safety Report NDA 21-316; P-002, dated 06-February-2003]

For a complete listing of all changes proposed in this labeling supplement, please refer to: Andrx Labs, Inc., SNDA 21-316; SLR 006, dated 23-December-2002.

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[1] Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM for the AFCAPS/TexCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS.TexCAPS. JAMA 1998;270(20):1615-1622.

B. Background

Altocor [lovastatin extended-release (XL)] is an extended-release formulation of lovastatin. Lovastatin immediate-release [lovastatin (IR)], as Mevacor, has been commercially available since 1987. Lovastatin is a member of the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor family of medications, also known as statin medications. Lovastatin is administered orally as an inactive lactone, which is hydrolyzed to its active form, the corresponding beta-hydroxyacid. The mechanism of action for the beta-hydroxyacid, which is common to all the statin medications, is as a competitive inhibitor of the HMG-CoA reductase enzyme. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the intracellular synthesis of cholesterol. The liver is the principal site of action for lovastatin. Preclinical and clinical data show that lovastatin can suppress cholesterol synthesis and up-regulate the number of hepatic LDL receptors[2], leading to the increased uptake of LDL-C from the systemic circulation by hepatic cells and reduced plasma levels of LDL-C.

Findings from PK studies with lovastatin XL show that relative to lovastatin IR:

- Lovastatin XL has delayed and extended-release properties
- Lovastatin XL had a more prolonged T_{max} and a lower C_{max}
- Lovastatin XL has a greater bioavailability of the prodrug lovastatin, but has equivalent bioavailability of the active drug lovastatin acid and the total and active inhibitors of HMG-CoA reductase
- Food decreases the bioavailability of lovastatin XL, whereas food increases the bioavailability of lovastatin IR

Findings from PD studies with lovastatin XL compared to lovastatin IR at doses of 20 mg and 60 mg show that lovastatin XL and lovastatin IR were nearly pharmacodynamically equivalent in LDL-C, TG and TC-lowering, and HDL-raising.

Lovastatin XL and IR are approved as:

- Treatments to reduce TC and LDL-C in familial and non-familial forms of primary hypercholesterolemia and mixed dyslipidemia (Fredrickson types IIa and IIb);
- Primary preventives of CHD in patients with average to moderately elevated TC and LDL-C, and below average HDL-C to reduce the risk of myocardial infarction (MI), unstable angina, and coronary revascularization procedures; and
- Treatments to slow the progression of coronary atherosclerosis in patients with established CHD

[2] Bradford RH, Shear CL, Chremos AN, Dujovne C, Downton M, Franklin FA, Gould AL, Hesney M, Higgins J, Hurley DP, Langendorfer A, Nash DT, Pool JL, Schnaper H. Expanded clinical evaluation of lovastatin (EXCEL) study results. Arch Intern Med 1991;151:43-49.

II. Review of Labeling Supplement Request

The sponsor's proposed changes to the Altocor label are of 1 of 3 types:

1. Changes for consistency with Mevacor label
2. Correction of typos and minor editing changes, and
3. Changes that differ from the existing Mevacor label

These types of changes will be considered individually.

A. Changes for Consistency with Mevacor Label

The sponsor is proposing the following changes to the Altocor label for consistency with the Mevacor label (innovator drug). For all of these changes, the proposed wording is identical to the wording currently present in the Mevacor label (version dated June-2002). Thus, as this wording has already been reviewed and approved for the innovator drug, this Reviewer has no objection to the inclusion of the same wording in the Altocor label. These changes are summarized as follows:

1. Clinical Pharmacology Section, Pharmacokinetics and Drug Metabolism, Metabolism Subsection (page 6 of annotated label)

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

2. Warnings Section, Myopathy/Rhabdomyolysis Subsection (pages 18-23 of the annotated label)

The sponsor has proposed removing the current wording in the Skeletal Muscle subsection in the Altocor label in its entirety and replacing it with identical wording to the wording found in the Mevacor label myopathy/rhabdomyolysis subsection [please see this SNDA submission for wording].

Note: As the Myopathy/Rhabdomyolysis subsection is proposed to replace the Skeletal Muscle subsection, editing changes reflecting this subsection name change appear in multiple places throughout the proposed Altocor label. There are no objections to these editing changes, and they will not be noted further in this review.

3. Precautions Section, Drug Interactions Subsection (pages 25-26 of the label)

The sponsor has proposed removing from the Altocor label, in their entirety, the current wording in the Drug Interactions subsection under the headers: gemfibrozil and other fibrates, lipid-lowering doses of niacin, and CYP3A4 Interactions. The sponsor has proposed replacing these items with identical wording to the wording found in the Mevacor label under the headers: CYP3A4 Interactions, Interactions with lipid-lowering drugs that can cause myopathy when given alone, and Other drug interactions, Amiodarone or Verapamil [please see this SNDA submission for wording].

4. Adverse Reactions Section, Hypersensitivity Reactions (page 34 of the label)

Proposed addition of "dermatomyositis" to listing of hypersensitivity reactions seen with lovastatin or other drugs in this class. Dermatomyositis appears in the current version of the Mevacor label.

5. Dosage and Administration Section (page 35 of the label)

The following additions to the Dosage and Administration section (page 35) have been proposed (additions in underlined text and deletions in ~~strikethrough~~ text):

"Dosage in Patients Taking Cyclosporine
In patients taking cyclosporine concomitantly with ALTOCOR™ (see **WARNINGS**, *Myopathy/Rhabdomyolysis*~~*Skeletal Muscle*~~), therapy should begin with 10 mg of ALTOCOR™ and should not exceed 20 mg/day.

Dosage in Patients Taking Amiodarone or Verapamil
In patients taking amiodarone or verapamil concomitantly with ALTOCOR™, the dose should not exceed 40 mg/day (see WARNINGS, *Myopathy/Rhabdomyolysis and* PRECAUTIONS, *Drug Interaction, Other Drug Interactions*).

Concomitant Lipid-Lowering Therapy

Use of ALTOCOR™ with fibrates or niacin should generally be avoided. However, if ALTOCOR™ is used in combination with gemfibrozil, other fibrates, or lipid-lowering doses (>1 g/day) of niacin, the dose of ALTOCOR™ should ~~generally~~ not exceed 20 mg (see **WARNINGS**, *Myopathy/Rhabdomyolysis*~~*Skeletal Muscle*~~ and **PRECAUTIONS**, *Drug Interactions*)."

B. Correction of Typos and Minor Editing Changes

The sponsor is proposing the following correction of typos and minor editing changes to the Altocor label. This Reviewer has no objection to any of these changes. These changes are summarized as follows:

1. Precautions Section, Information for Patients Subsection (page 24 of the label)

The sponsor has proposed adding "or cut" to the existing sentence (additions in underlined text and deletions in ~~strikethrough~~ text) "The ALTOCOR™ Extended-Release Tablets should be swallowed whole and not chewed, ~~or~~ crushed, or cut" as physically damaging the tablet may alter its controlled-release characteristics.

2. Adverse Reactions Section, (pages 31 and 33 of the label)

Typo corrections of "in" by "as" (preceding Table VII on page 31), and removal of "(1)" (preceding AFCAPS/TexCAPS header on page 33) are proposed.

3. Revision Date (page 36 of the label)

The revision date has been revised to —— to reflect this version of the Altocor label.

C.

The sponsor is proposing changes to the Altocor label

As rationale for the proposed change, the sponsor has submitted the following [from NDA 21-316; SLR 006 submission, Attachment 2, dated 23-December-2002]:

"This request is supported by Andrx Labs expanded data, including both new data from ongoing studies and those completed after the original Altocor NDA was approved, as well as post-marketing data.

The materials submitted by the sponsor in support of this proposed change, including post-marketing surveillance data for Altocor, recent clinical trials results from completed and ongoing trials with Altocor, and data from the public domain are summarized as follows:

1. Post-Marketing Data

The sponsor states that:

"The post-market experience, in particular, shows that

but carries significant

Post-marketing databases cannot be reliably used to calculate incidence rates as the true denominator of patient exposure is not known, and as Adverse Events (AEs) are spontaneously reported, it is unlikely that all AEs occurring during this time period were reported to the database. Thus, the Division must rely on properly conducted clinical

trials for the estimation of incidence rates. In addition, the Altocor post-marketing database is quite small compared to the number of patients exposed to statin medications in the United States and worldwide. From the sponsor's most recent Periodic Safety Report [NDA # 21-316; P-002, dated 23-January-2003], for the period 26-Sept-2002 to 25-Dec-2002, the sponsor has estimated that 42,144 prescription were sold in the United States as of 20-Dec-2002. The sponsor approximates that this would represent approximately

The sponsor also did not submit to support the above statement.

2. Safety Data from Altocor's NDA Clinical Program

Patient exposures from the Altocor initial NDA clinical program are as follows [from Pariser A, MD, Medical Officer's Review of NDA 21-316; 000, dated 09-Jan-2002]:

"In the lovastatin XL clinical program, a total of 588 patients were exposed to lovastatin XL, 354 patients were exposed to Mevacor, and 34 patients were exposed to placebo [Note: This does not include patients in the single-dose Phase I studies]. There were 427 patients exposed to lovastatin XL for at least 12 weeks, and 233 patients exposed to lovastatin XL for 24 weeks or more. The majority of patients were exposed to lovastatin XL in the 2 large, controlled studies. For the controlled studies, mean exposure was similar across the treatment groups, with mean exposures of 11.6 weeks for the lovastatin XL groups, 12.0 weeks for the placebo group, and 11.7 weeks for the Mevacor groups. Exposures by clinical study are summarized in the following table

Table 1: Patient Exposure to Lovastatin XL, Mevacor, and Placebo in the Altocor Clinical Program submitted to the NDA

		Treatment									
		Lovastatin XL					Mevacor				
Study	Placebo	10 mg	20 mg	40 mg	60 mg	All	20 mg	40 mg	60 mg	All	Total
Controlled Studies											
146-009	34	35	34	33	36	138	-	-	-	-	172
146-010	-	-	162	-	167	329	166	-	163	329	358
Total	34	35	196	33	203	467	166	-	163	329	530
Uncontrolled Studies											
146-011*	-	-	-	128	237	365	-	-	-	-	365
Total	-	-	-	196	237	433	-	-	-	-	433
Overall Total	**34**	**35**	**196**	**223**	**302**	**588#**	**166**	**25**	**163**	**354**	**624**

*majority of patients exposed to lovastatin XL in studies 146-009 and 146-010
#includes additional 28 patients previously exposed to placebo in study 146-009, exposed to lovastatin XL in 146-011"

From the pooled safety results in these clinical studies, 1 patient exposed to Altocor (0.2%) and 0 patients exposed to Mevacor had notable ALT and AST elevations, defined as >3X ULN on 2 consecutive occasions. This 1 patient had ALT and AST elevations in the context of being hospitalized for cholecystitis, choledocolithiasis, and pancreatitis.

The sponsor reports no other cases of notable liver enzyme elevations in ongoing and completed (since NDA approval) studies with Altocor, including in the high-dose (HD) clinical program, which exposes patients to doses of Altocor or 100 mg to 120 mg per day. This program involves completed and ongoing Phase 2 and Phase 3 trials in approximately 760 patients, approximately 303 of whom have been exposed to Altocor for ≥162 days (23.1 weeks).

3. Data from Publications (Public Domain)

a) The EXCEL Study

The sponsor cites results from the Expanded Clinical Evaluation of Lovastatin (EXCEL) Study Results: the One-Year[3] and Two-Year[4] follow-up results. Briefly, EXCEL was a multi-center, double-blind, diet- and placebo-controlled study of the efficacy and safety of lovastatin in 8,245 patients with moderate hypercholesterolemia. Patients were randomly assigned to lovastatin 20 mg, 40 mg (as 40 mg qDay or 20 mg BID), or 80 mg (40 mg BID) or placebo for 48 weeks. Long-term follow-up of 25% of the clinical centers followed patients for an additional year (Year 2) of treatment, with 977 patients entered into Year 2. The Year 2 cohort does not represent randomized treatment groups and includes a relatively small placebo group. Each patient continued to maintain the double-blind assignment from Year 1 in his/her original treatment group.

Year 1 results showed that 1,642 to 1,663 patients were randomized into each of the 5 treatment groups. The incidence of serum transaminase level elevations of potential clinical importance, defined as successive serum transaminase level elevations >3X ULN, were 0.1% of patients receiving placebo, 0.1% of patients receiving lovastatin 20 mg/day, 0.9% of patients in each of the 40 mg groups, and 1.5% of patients in the 80 mg/day group. ($p<.001$ for trend with increasing dose). Of the 47 patients who experienced their first liver enzyme elevation (ALT, AST, or both) >3X ULN, 6 patients experienced this elevation within the first 90 days of treatment. Thereafter, the elevations occurred sporadically over time. After discontinuation of study drug, 45 of 47 patients had transaminase levels decrease, 29 of whom returned to within normal limits (WNL).

The incidences of single transaminase level elevations >3X ULN and single and successive elevations >2X ULN were no higher in the patients receiving 20 mg/day of

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[3] Bradford RH, Shear CL, Chremos AN, Dujovne C, Downton M, Franklin FA, Gould AL, Hesney M, Higgins J, Hurley DP, Langendorfer A, Nash DT, Pool JL, Schnaper J. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. Arch Intern Med 1991;151:43-49.

[4] Bradford RH, Shear CL, Chremos AN, Dujovne CA, Franklin FA, Grillo RB, Higgins J, Langendorfer A, Nash DT, Pool JL, Schnaper H. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results: Two-year efficacy and safety follow-up. Am J Cardiol 1994;74:667-673.

lovastatin than in the placebo group. These incidences rose progressively in the groups receiving 40 mg and 80 mg/day of lovastatin. The incidences of serum transaminase level elevations in Year 1 of the EXCEL study are summarized in the following table

Table 2: EXCEL Year 1 Incidence of Serum Transaminase Elevations

		Lovastatin Dose			
	Placebo	**20 mg qD**	**40 mg qD**	**20 mg BID**	**40 mg BID**
Elevation					
>3X ULN					
Successive, n (%)	2 (0.1)	2 (0.1)	12 (0.9)	11 (0.9)	20 (1.5)
Single, n (%)	15 (1.2)	10 (0.8)	22 (1.9)	21 (1.8)	42 (3.2)
>2X ULN					
Successive, n (%)	7 (0.5)	6 (0.5)	17 (1.3)	21 (1.7)	42 (3.0)
Single, n (%)	28 (2.2)	28 (2.1)	44 (3.7)	54 (4.1)	81 (6.1)

Year 2 results showed a total of 977 patients were entered into the Year 2 phase of the study. Cholesterol treatment goals were required for eligibility into the Year 2 phase of the study, and eligibility was associated with lovastatin treatment and was dose-dependent. Fifty-seven percent (57%) to 80% of lovastatin-treated patients, but only 14% of placebo-treated patients, met the required LDL-C goal for entry into the Year 2 phase. A total of 977 patients enrolled, as follows: 47 patients from the placebo group, 186 patients from the lovastatin 20 mg group, 231 patients from the 40 mg qD group, 255 patients from the 20 mg BID group, and 258 patients from the 40 mg BID group.

No patient was diagnosed as having clinical hepatitis, and no evidence of progressive liver disease was found during Years 1 and 2. Only 1 patient was found to have successive transaminase elevations >3X ULN (ALT but not AST). The ALT returned to WNL within 2 weeks after discontinuing lovastatin in this patient. The cumulative incidence of successive transaminase elevations >3X ULN, based on life-table analyses for the 8,245 patients followed up in Year 1 and the 977 patients followed up in Year 2 were 0.1% in the placebo and lovastatin 20 mg groups, 0.9% in the 2 groups given lovastatin 40 mg/day (20 mg BID and 40 mg qD), and 1.9% in patients given lovatastin 80 mg/day. Seven (7) of the 48 cases of transaminase elevations were observed before Week 15 (1 in the placebo group, 4 in the lovastatin 40 mg/day, and 2 in the lovastatin 80 mg/day). There were 40 patients with transaminase elevations in the interval between Week 15 and Week 51. Findings of single serum transaminase elevations >3X ULN and single and successive elevations >2X ULN are summarized in the following table

Table 3: EXCEL Year 1 and Year 2 Cumulative Incidence of Serum Transaminase Elevations

		Lovastatin Dose			
	Placebo	20 mg qD	40 mg qD	20 mg BID	40 mg BID
Elevation					
>3X ULN					
Successive					
Year 1, n (%)	2 (0.1)	2 (0.1)	12 (0.9)	11 (0.9)	20 (1.5)
Year 1 & 2, n (%)	2 (0.1)	2 (0.1)	12 (0.9)	11 (0.9)	21 (1.9)
Single					
Year 1, n (%)	15 (1.2)	10 (0.8)	22 (1.9)	21 (1.8)	42 (3.2)
Year 1 & 2, n (%)	16 (3.6)	10 (0.8)	23 (2.2)	22 (1.9)	45 (4.9)
>2X ULN					
Successive					
Year 1, n (%)	7 (0.5)	6 (0.5)	17 (1.3)	21 (1.6)	42 (3.0)
Year 2, n (%)	7 (0.5)	6 (0.5)	18 (1.7)	21 (1.6)	43 (3.4)
Single					
Year 1, n (%)	28 (2.2)	28 (2.1)	43 (3.3)	53 (3.8)	81 (6.1)
Year 1 & 2, n (%)	29 (2.9)	29 (2.5)	48 (5.3)	57 (5.3)	85 (7.0)

b) AFCAPS/TexCAPS

Briefly, AFCAPS/TexCAPS was a randomized, double-blind, placebo-controlled study of the efficacy and safety of lovastatin 20-40 mg/day or placebo in 6,605 patients (5,608 men and 997 women) with average TC and LDL-C and below average HDL-C. Patients were started on lovastatin 20 mg/day or matching placebo, and titrated to lovastatin 40 mg/day (or matching placebo) if their LDL-C level was >2.84 mmol/L (110 mg/dL) at the 3-month study visit. The blind was maintained during titration. The primary outcome measures were first acute major coronary event defined as fatal or nonfatal MI, unstable angina, or sudden cardiac death. An extensive safety evaluation was performed prior to treatment, at 1 year, and at each subsequent year-end visit. Average follow-up was for 5.2 years. Lovastatin significantly reduced the risk for the first acute major coronary event in men and women (RR 0.63; p<.001), MI (RR 0.60; p=.002), unstable angina (RR 0.68; p=.02), coronary revascularization procedures (RR 0.67; p=.001), coronary events (RR 0.75; p=.006), and cardiovascular events (RR 0.75; p=.003).

Safety results were notable for consecutive elevations of >3X ULN in either AST or ALT being rare, and the incidence was similar in both treatment groups: 18 of 3,242 patients (0.6%) in the lovastatin group and 11 of 3,248 patients (0.3%) in the placebo group. Examination of these elevation by final dose for those patients who were titrated also revealed no significant trends: 11 of 1,585 patients (0.7%) receiving lovastatin 20 mg/day and 7 of 1,657 patients (0.4%) receiving lovastatin 40 mg/day had consecutive elevations of AST or ALT >3X ULN.

c) Lovastatin 5-Year Safety and Efficacy Study

The Lovastatin 5-year Safety and Efficacy Study[5] was a multi-center study of patients with hypercholesterolemia (Fredrickson types IIa and IIb), who were at high-risk of MI either due to heterozygous familial hypercholesterolemia, or due to LDL-C >5.6 mmol/L (215 mg/dL), LDL-C >4.9 mmol/L (190 mg/dL) plus other coronary risk factors, or >4.3 mmol/L (165 mg/dL) with clinically manifest coronary atherosclerosis. All patients were originally in one of four multi-center controlled studies of 12-18 weeks duration that compared the short-term efficacy, safety, and tolerability of lovastatin to placebo, cholestyramine, or probucol (n =752 patients). After completion of these studies, all but 7 patients proceeded into a long-term open extension study, regardless of initial treatment assignment (lovastatin or control drug). This study describes data from the extension study.

After completion of the original controlled studies, drug treatment was open-label. Lovastatin was titrated in each patient at the beginning of the open-label phase. All patients received lovastatin 20 mg/D and increased, if necessary, to 40 mg/D, then 80 mg/D. The goal of treatment was LDL-C of 3.6 mmol/L (140 mg/dL) or less, or 3.1 mmol/L (120 mg/dL) in patients with known CAD. If LDL-C fell to <2.3 mmol/L (90 mg/dL), the dose of lovastatin was reduced. If further lipid lowering was required, other lipid-lowering agents could be added.

A total of 745 patients were enrolled for a median of 5.2 years (mean 4.8 years). Eighty percent (80%) of these patients completed the study, 13% were unavailable for follow-up or could not comply with study procedures, and 3% were discontinued for AEs. At the end of the study, the average daily dose of lovastatin was 70 mg/D, with 77% of patients receiving lovastatin 80 mg/D, 2% receiving 60 mg/D, 17% receiving 40 mg/D, and 4% receiving 20 mg/D. Fifty-eight percent (58%) had taken 1 or more other lipid-lowering medications concomitantly, but only 38% were still receiving the concomitant therapy at the last visit. Fifty percent (50%) of patients took bile acid sequestrants, 18% took niacin, and 3% took gemfibrozil.

Safety results were notable for 21 patients being discontinued for drug-attributable AEs. The most common cause was for asymptomatic, marked (>3X ULN) increases in transaminases, which occurred in 10 patients. Eight (8) of these 10 patients had their first transaminase elevation >3X ULN in the first year after starting lovastatin therapy. In the remaining 2 patients, the first elevation occurred at 13 and 22 months. Following discontinuation of lovastatin therapy, the transaminase values were WNL (7 patients) or fell to near-normal range (3 patients). Fourteen (14) additional patients had elevations of one or both transaminase values (AST, ALT, or both) to >3X ULN on 2 or more consecutive visits, but were not withdrawn from the study. In 5 patients, treatment was interrupted and subsequently resumed, and in 3 patients the dose of lovastatin was reduced. In 12 of these 14 patients, the transaminase values returned to normal or

[5] Lovastatin Study Group I through IV. Lovastatin 5-year safety and efficacy study. Arch Intern Med 1993;153:1079-1087.

slightly elevated values during continued therapy. The remaining 2 patients were unavailable for follow-up.

The safety results for transaminase elevations in this study are difficult to interpret. The incidence rates for transaminase elevations regardless of causality were not reported, transaminase data were not presented by dose of lovastatin received, nor were contributing factors, such as by patients taking concomitant therapy known to cause transaminase elevations (e.g., niacin) reported.

d) The Liver and Lovastatin Paper, and Defining Patient Risks from Expanded Preventive Therapies (Toman KG)

The Liver and Lovastatin[6] paper was a review by Tolman KG summarizing (for lovastatin) "the experience to date starting with animal toxicology studies, through premarketing and postmarketing trials, and finally, through 24 million patient-years of postmarketing use." The focus of the paper was on ALT levels. Defining Patient Risks from Expanded Preventive Therapies[7] paper reviewed all commercially available lipid-lowering agents and their effect on the liver.

The clinical experience summarized in both papers included premarketing clinical trials conducted with lovastatin. These trials showed that increased ALT, defined as increases ≥3X ULN, was reported in 1.9% of patients in Phase IIb trials and appeared to be dose related. Increased ALT was also reported as a drug-related event in 3.1% of patients treated with lovastatin 40-80 mg/day in Phase III trials, which was comparable to the incidence of ALT elevations seen with comparator agents, including cholestyramine (3.4%) and probucol (3.1%). Increases in transaminases >3X ULN resulted in 15 of the 2,045 lovastatin-treated patients (0.7%) being discontinued from study drug.

The postmarketing studies summarized in both papers included the EXCEL study and AFCAPS/TexCAPS, which have been previously summarized above, and will not be re-reviewed.

The author concluded in these reviews that:

- The transaminase elevations seen with lovastatin treatment were seen only at doses of lovastatin ≥40 mg/D, did not appear to be associated with hepatic injury, and, in most patients, resolved spontaneously without a change in medication.
- Similar changes were seen with Zocor (simvastatin) in the 4S study
- Minor elevations in ALT have been seen with all the other cholesterol-lowering agents and appear to be dose related.
- Histologic injury does not seem to occur with elevations in ALT, but rather reflect simple chemical changes in ALT or unmask underlying chronic liver disease
- Monitoring in the postmarketing clinical trials produced a high rate of false-positive results. Monitoring is effective only if it provides a meaningful period of time during which a patient can be rescued from irreversible liver damage.

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[6] Tolman KG. The liver and lovastatin. Am J Cardiol 2002;89:1374-1380.
[7] Tolman KG. Defining patient risks from expanded preventive therapies. Am J Cardiol 2000;85:15E-19E.

The author summarized by saying that the high rate of false-positive outcomes combined with the low likelihood of producing a favorable hepatic outcome suggests [redacted] Transient, minor, reversible elevations of ALT are characteristic of all the lipid-lowering agents. This appears to be a pharmacodynamic characteristic and is probably related to lowering of cholesterol levels.

III. Conclusions

There are no objections to the sponsor's proposed changes to the safety section of the Altocor label to incorporate the recent changes to the Mevacor (innovator drug) package insert, and to include the minor editing changes (changes reviewed in detail above). These changes have already been reviewed and approved for Mevacor. [redacted]

The safety data with Altocor included pre-NDA approval studies with Altocor with exposures to Altocor of <500 patients for 12 weeks, and <250 patients for 24 weeks or more, and from spontaneously reported post-marketing surveillance data with Altocor in approximately 4,000 patients. [redacted]

The data from the public domain, in the form of published journal articles from the Medical literature, refer to studies conducted with Mevacor. As the overwhelming majority of liver safety data for lovastatin was conducted for Mevacor, and as the current labeling for Altocor relies on the available data for Mevacor, [redacted]

Additional reference is made by the sponsor to Zocor's (simvastatin) label, although no safety data for Zocor (other than a reference to the label) were included in the submission.

IV. Recommendations

It is the recommendation of this Reviewer that the sponsor receive an approvable letter for the proposed changes to the Altocor label. It is recommended that approval be given to the proposed changes including the approved, recent revisions to the safety section of the Mevacor label, and the minor editing changes as outlined above. However, the proposed change

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/s/

Anne Pariser
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MEDICAL OFFICER

Mary Parks
5/21/03 03:24:33 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-316/S-006

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

Division of Metabolic and Endocrine Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 21-316/S-006

Name of Drug: Altocor (lovastatin) Extended-Release Tablets, 10mg, 20mg, 40mg, and 60mg

Applicant: Andrx Laboratories, Inc.

Material Reviewed:

Submission Date(s): December 23, 2002, (electronic) and July 30, 2003, (paper) draft labeling.

Background and Summary

This supplement was submitted on December 23, 2002, to enhance the safety sections, making the PI more congruent with the recent changes to the Mevacor® PI and [redacted] An Approvable letter was issued on [redacted] On July 29, 2003, an amendment to supplement-006 was submitted, accepting the Agency's recommendations.

Review

The proposed PI was compared to the approved PI (supplement-001, Acknowledged and Retained on February 7, 2003). Other than the statement revision that the Agency recommended, they are identical.

Conclusions

An Approval letter should be drafted.

Valerie Jimenez
Regulatory Project Manager

Supervisory Comment/Concurrence:

_____

Enid Galliers
Chief, Project Management Staff

Drafted: V.J./August 19, 2003
Revised/Initialed: E.G./September 8, 2003
Finalized: September 8, 2003
Filename: C:\Data\Altocor-N2116.SLR006.doc

CSO LABELING REVIEW

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/s/

Valerie Jimenez
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Enid Galliers
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Division of Metabolic & Endocrine Drug Products

PROJECT MANAGER LABELING REVIEW

Application Number: NDA 21-316/S-006

Name of Drug: Altocor (lovastatin) Extended-Release Tablets, 10mg, 20mg, 40mg, and 60mg

Sponsor: Andrx Laboratories Inc.

Materials Reviewed:

Submission Date(s): December 23, 2003, draft labeling for the package insert (PI).

Background and Summary

This application was submitted to make the PI more congruent with the recent changes of the Mevacor® PI

Review

The proposed PI was compared to the currently approved PI (supplement-001, Acknowledged and Retained on February 7, 2003). Other than the revisions described in the medical officer's review, the only change that has been made is to update the revision date from , they are identical.

This is an acceptable revision.

Note: In the May 21, 2003 Medical Officer's review of the labeling supplement, label changes for consistency with Mevacor® label, corrections of typos and minor editing changes, and changes that differ from the existing Mevacor® label have been reviewed individually. All revisions were found acceptable

Conclusion

An Approval letter should be drafted pending revision of the WARNINGS section to that which is currently approved. The text should read:

"It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation of dose, and periodically thereafter (e.g., semiannually)".

Valerie Jimenez
Regulatory Project Manager, HFD-510

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/s/

Valerie Jimenez
6/4/03 11:44:41 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-316/S-006

PRIOR APPROVAL SUPPLEMENT

Andrx Laboratories Inc.
Attn: Nicholas J. Farina, Ph.D.
Vice President, Regulatory Affairs
401 Hackensack Avenue, 9th Floor
Hackensack, NJ 07601

Dear Ms. Farina:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Altocor™ (lovastatin) Extended Release Tablets
NDA Number:	21-316
Supplement number:	S-006
Date of supplement:	December 23, 2002
Date of receipt:	December 24, 2002

This supplemental application proposes to change the package insert (PI) for Altocor™ to enhance the safety sections, making the PI more congruent with the recent changes of the Mevacor®.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 22, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 22, 2003.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any question, call me at (301) 827-6412.

Sincerely,

{See appended electronic signature page}

William C. Koch, R.Ph.
Regulatory Project Manger
Division of Metabolic & Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

William Koch
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