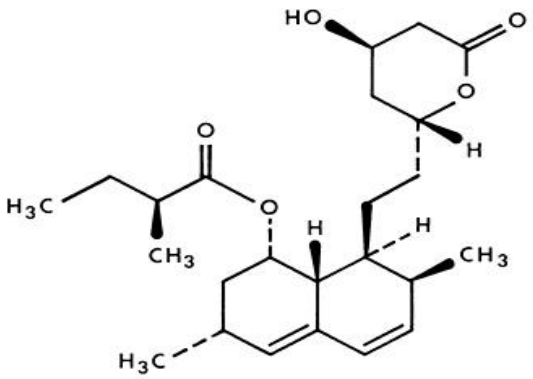
ALTOCOR™ Extended-Release Tablets
(Lovastatin)

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)

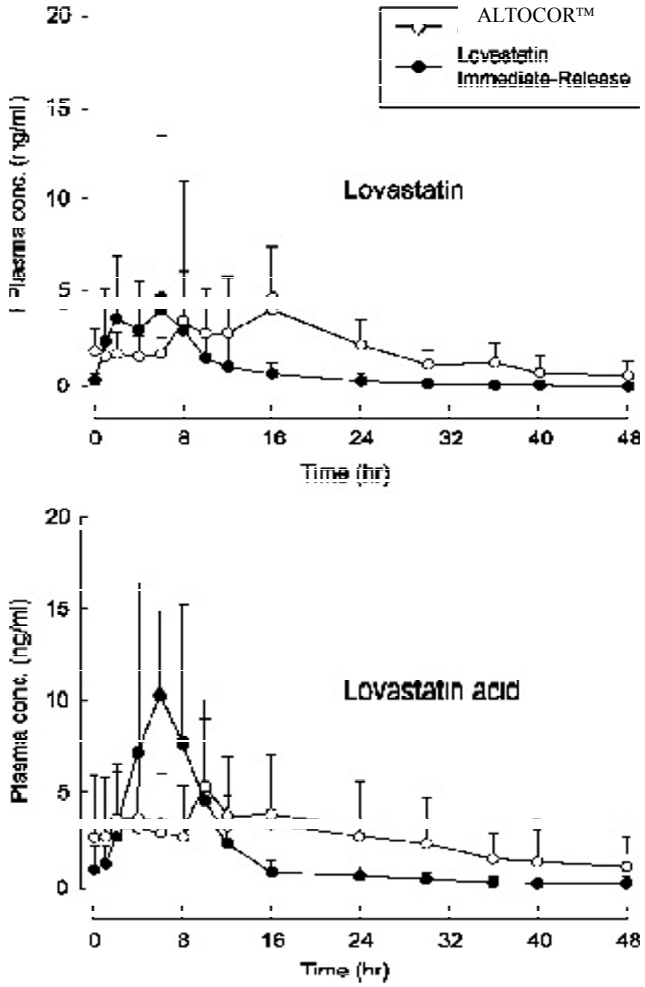
Drug	C_{max} (ng/mL)				C_{min} (ng/mL)				T_{max} (h)		$AUC_{0\text{-}24hr}$ (ng·h/mL)			
	L	LA	TI	AI	L	LA	TI	AI	L	LA	L	LA	TI	AI
ALTOCOR™ 40 mg*	5.5	5.8	17.3	13.4	2.6	3.1	9.1	4.3	14.2	11.8	77	87	263	171
Lovastatin IR 40 mg**	7.8	11.9	36.2	26.6	0.4	0.7	2.4	2.1	3.3	5.3	45	83	252	186

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.

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**.

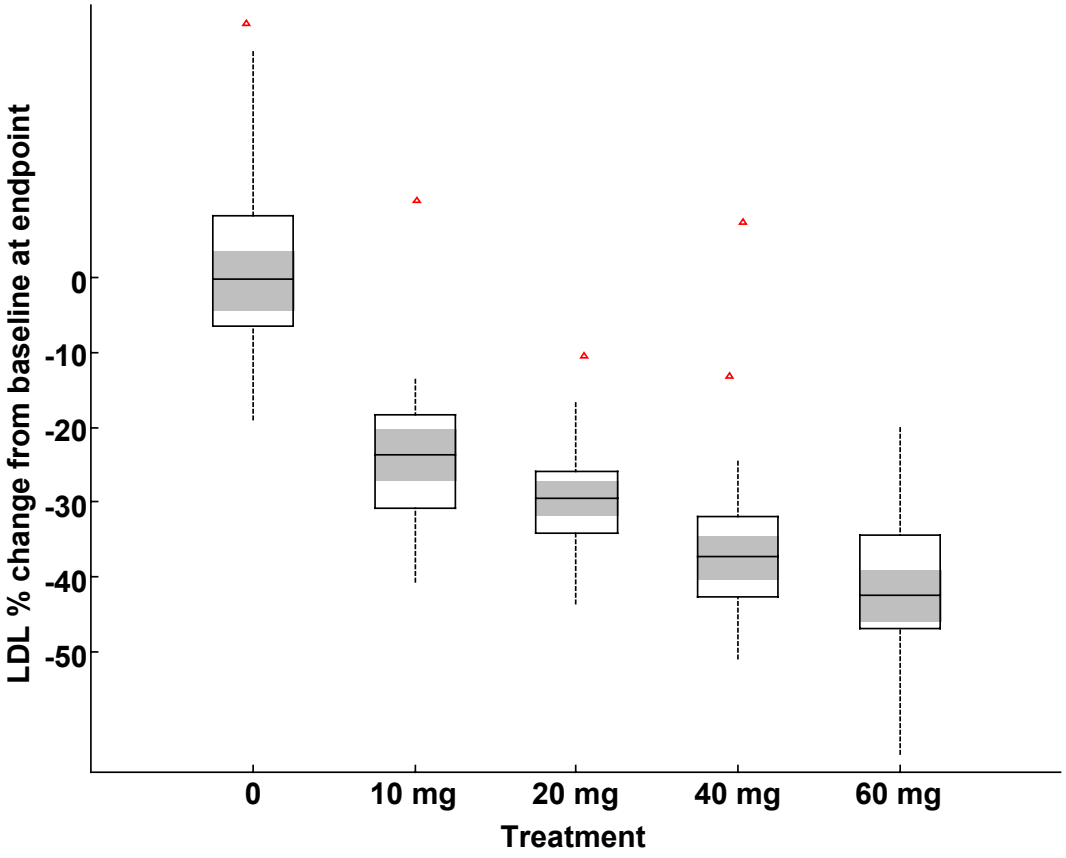
Table III
ALTOCOR™ vs. Placebo
(Mean Percent Change from Baseline After 12 Weeks)*

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)

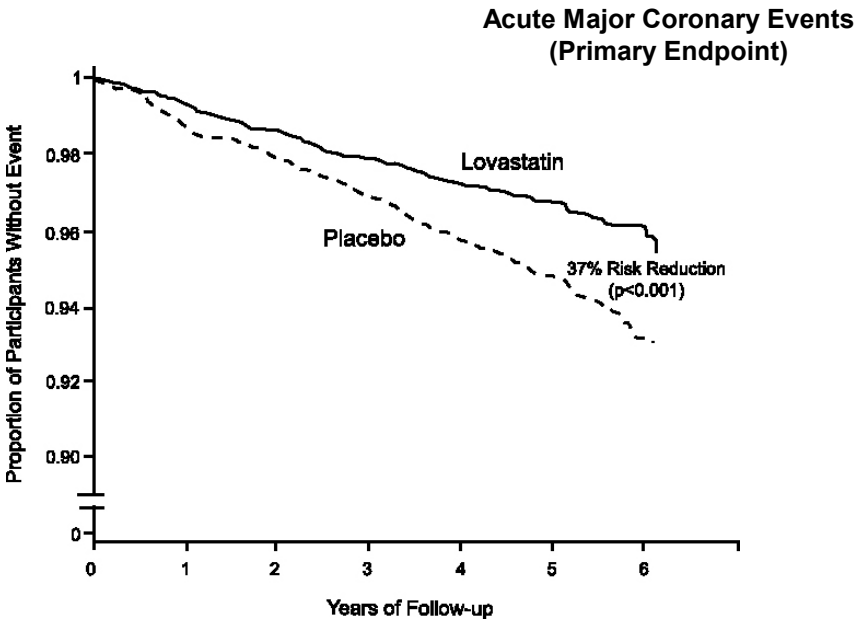
The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), a double-blind, randomized, placebo-controlled, primary prevention study, demonstrated that treatment with lovastatin immediate-release decreased the rate of acute major coronary events (composite endpoint of myocardial infarction, 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:

LDL-C = Total-C - [0.2 × (TG) + HDL-C]

For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In hypertriglyceridemic patients, LDL-C may be low or normal despite elevated Total-C. In such cases, 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

Skeletal Muscle

Lovastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as muscle pain or weakness associated with grossly elevated creatine kinase [>10 × the upper limit of normal (ULN)]. **Rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, has been reported rarely and can occur at any time.** In the EXCEL study, there was one case of myopathy among 4,933 patients randomized to lovastatin 20 mg - 40 mg daily for 48 weeks, and 4 among 1,649 patients randomized to 80 mg daily. When drug treatment was interrupted or discontinued in these patients, muscle symptoms and creatine kinase (CK) increases promptly resolved. The risk of myopathy is increased by concomitant therapy with certain drugs, some of which were excluded by the EXCEL study design.

Myopathy caused by drug interactions.

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

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

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

Reducing the risk of myopathy.

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

Of the patients with rhabdomyolysis, many had complicated medical histories. Some had preexisting renal insufficiency, usually as a consequence of long-standing diabetes. In such patients, dose escalation requires caution. Also, as there are no known adverse consequences of brief interruption of therapy, treatment with ALTOCOR™ should be stopped a few days before elective major surgery and when any major acute medical or surgical condition supervenes

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

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

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

Liver Dysfunction

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

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 or crushed.

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

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.

Gemfibrozil and other fibrates, lipid-lowering doses (≥ 1 g/day) of niacin (nicotinic acid): These drugs increase the risk of myopathy when given concomitantly with lovastatin (see **WARNINGS**, *Skeletal Muscle*). There has been evidence to suggest that the increased risk of myopathy may be partly due to the pharmacokinetic interactions between gemfibrozil and lovastatin.

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

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

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

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

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 in ≥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		
		Placebo	ALTOCOR™	MEVACOR™
Randomized Patients, n =		**34**	**467**	**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**, *Skeletal Muscle*).

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%.

(1) 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**, *Skeletal Muscle*)

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

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

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

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

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

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.

Concomitant Lipid-Lowering Therapy

Use of ALTOCOR™ with fibrates or niacin should generally be avoided. However, if ALTOCOR™ is used in combination with fibrates or niacin, the dose of ALTOCOR™ should generally not exceed 20 mg (see **WARNINGS**, *Skeletal Muscle* and **PRECAUTIONS**, *Drug Interactions*).

Dosage in Patients with Renal Insufficiency

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

HOW SUPPLIED

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

Rev. date: 07/02 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.

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/s/

David Orloff
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