PRODUCT MONOGRAPH

PrRAN-LOVASTATIN

Lovastatin tablets, MFR standard

20 mg and 40 mg

Lipid metabolism regulator

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PRODUCT MONOGRAPH

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PHARMACEUTICAL / THERAPEUTIC CLASSIFICATION

Lipid metabolism regulator

ACTIONS AND CLINICAL PHARMACOLOGY

Lovastatin is a cholesterol-lowering agent isolated from a strain of *Aspergillus terreus.* After oral ingestion, lovastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxy acid form. This principal metabolite is a specific 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 reduces cholesterol production by the liver and induces some changes in cholesterol transport and disposition in the blood and tissues. The mechanism(s) of this effect is believed to involve both reduction of the synthesis of Low Density Lipoprotein (LDL), and an increase in LDL catabolism as a result of induction of the hepatic LDL receptors.

Lovastatin has complex pharmacokinetic characteristics (see **PHARMACOLOGY**).

Lovastatin is metabolized by the microsomal hepatic enzyme (Cytochrome P-450 isoform 3A4 system). The major active metabolites present in human plasma are the β-hydroxy acid of lovastatin, its 6ə-hydroxy, 6ə-hydroxymethyl, and the 6ə-exomethylene derivatives.

BIOAVAILABILITY

A randomized, two-way crossover, single-dose bioavailability study was conducted in fasting healthy, adult male subjects. The bioavailability of **RAN-LOVASTATIN** tablets, 20 mg, relative to Mevacor® tablets, 20 mg, was determined following a single 4 x 20 mg dose. The average values of the pharmacokinetic parameters, as well as ratio of means (with 90% confidence intervals) are listed in the following table:

Table 1:

Summary Table of the Comparative Bioavailability Study of **RAN-LOVASTATIN** vs Mevacor®, Lovastatin 20 mg tablets conducted under fasting conditions in 44 healthy adult male volunteers (from measured data)

Parameter	Lovastatin Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%) (90% Confidence Limits)
	RAN-LOVASTATIN	Mevacor®**	
AUCt (ng.h/mL)	73.61 90.52 (53.5)	80.31 95.44 (51.3)	92 (83-101)
AUCinf (ng.h/mL)	85.81 102.96 (49.5)	96.22 108.12 (44.4)	95 (86-105)
C_{max} (ng/mL)	4.82 5.55 (50.1)	5.00 6.06 (66.6)	96 (86-108)
T_{max}* (h)	4.62 (63.9)	4.55 (48.4)	---
$T_{½}$* (h)	13.78 (45.4)	12.25 (34.0)	---

**The T_{max} and $t_{½}$ parameters are expressed as the arithmetic means.*

***Mevacor® is manufactured by Merck Sharp and Dohme and was purchased in Canada.*

Conclusion: The 90% confidence intervals for the ln-transformed parameters AUCt, AUCinf and Cmax for lovastatin were within the 80-125% TPD acceptance range both before and after correction for measured content. Based on these results, **RAN-**

LOVASTATIN and Mevacor® (lovastatin) 20 mg tablets are considered bioequivalent under single-dose fasting conditions.

INDICATIONS AND CLINICAL USE

RAN-LOVASTATIN (lovastatin tablets) is indicated as an adjunct to diet, at least equivalent to the American Heart Association (AHA) Step 1 diet, for the reduction of elevated total and Low Density Lipoprotein Cholesterol (LDL-C) levels in patients with primary hypercholesterolemia (Types IIa and IIb),† when the response to diet and other nonpharmacological measures alone has been inadequate.

After establishing that the elevation in plasma lipids represents a primary disorder not due to secondary conditions such as poorly-controlled diabetes mellitus, hypothyroidism, the nephrotic syndrome, liver disease, or dysproteinemias, it should be determined that patients for whom treatment with lovastatin is being considered have an elevated LDL-C level as the cause for an elevated total serum cholesterol. This may be particularly relevant for patients with total triglycerides over 4.52 mmol/L (400 mg/dL) or with markedly elevated High Density Lipoprotein Cholesterol (HDL-C) values, where non-LDL lipoprotein fractions may contribute significantly to total cholesterol levels without apparent increase in cardiovascular risk. In general, LDL-C may be estimated according to the following equation:

LDL-C (mmol/L) = Total cholesterol - [(0.37 x triglycerides)+ HDL-C] ††

LDL-C (mg/dL) = Total cholesterol - [(0.16 x triglycerides) + HDL-C]

When total triglycerides are greater than 4.52 mmol/L (400 mg/dL) this equation is not applicable. In such patients, LDL-C may be obtained by ultra-centrifugation.

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† A disorder of lipid metabolism characterized by elevated serum cholesterol levels in association with normal triglyceride levels (Type IIa) or with increased triglyceride levels (Type IIb).

Fredrickson DS, Levy RI, Lees RS. Fat transport in lipoproteins – An integrated approach to mechanisms and disorders. N Engl. J. Med 1967;276:148-56

†† DeLong D, et al. A comparison of methods. J A M A 1986;256:2372-77.

Lovastatin was also found to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total and LDL-cholesterol to target levels. In two trials including this type of patients*, i.e. in a secondary prevention intervention, lovastatin monotherapy was shown to slow the progression of coronary atherosclerosis as evaluated by computerized quantitative coronary angiography (QCA). This effect, however, was not accompanied by an improvement in the clinical endpoints (death, fatal/nonfatal myocardial infarction, hospitalization for unstable angina, and coronary revascularization procedure [PTCA and CABG] within the 2 - 2 ½ yearsə period of treatment. These trials, however, were not designed to demonstrate a reduction in the risk of coronary morbidity and mortality.

The effect of lovastatin on the progression of atherosclerosis in the coronary arteries has been corroborated by similar findings in another vasculature. In a trial** including hyperlipidemic patients with early, asymptomatic carotid lesions and without known coronary artery disease, the effect of therapy with lovastatin on carotid atherosclerosis was assessed by B-mode ultrasonography.

There was a significant regression of carotid lesions in patients receiving lovastatin alone compared to those receiving placebo alone. The predictive value of changes in the carotid vasculature 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). This trial should be viewed as supportive and complementary to the others mentioned above. However, it was not powered to demonstrate a reduction in the risk of coronary morbidity and mortality. A larger trial of longer duration is needed to clarify the effect of lovastatin in monotherapy on clinical events (see WARNINGS, HUMAN PHARMACOLOGY, Clinical Studies, and SELECTED BIBLIOGRAPHY).

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* Canadian Coronary Atherosclerosis Intervention Trial (CCAIT). Monitored Atherosclerosis Regression Study (MARS).
** The Asymptomatic Carotid Artery Progression Study (ACAPS)

CONTRAINDICATIONS

- Hypersensitivity to any component of this medication.
- Active liver disease or unexplained persistent elevations of serum transaminases.
- Pregnancy and lactation (see also **PRECAUTIONS**).

WARNINGS

Pharmacokinetic interactions:

The use of HMG-CoA reductase inhibitors has been associated with severe myopathy, including rhabdomyolysis, which may be more frequent when they are co-administered with drugs that inhibit the cytochrome P-450 enzyme system. Lovastatin is metabolized by the cytochrome P-450 isoform 3A4 and as such may interact with agents which inhibit this enzyme (see Myopathy and **PRECAUTIONS**, Drugs Interactions and Cytochrome P-450 Inhibitors).

Myopathy:

Lovastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as muscle pain or weakness associated with grossly elevated CPK (> 10X the upper limit of normal). Rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, has been reported rarely and can occur at any time. In the Expanded Clinical Evaluation of Lovastatin (EXCEL study), there was one case of myopathy among 4933 patients randomized to lovastatin 20-40 mg daily for 48 weeks, and 4 among 1649 patients randomized to 80 mg daily. When drug treatment was interrupted or discontinued in these patients, muscle symptoms and CPK 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 appears to be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Lovastatin and other HMG-CoA reductase inhibitors are metabolized by the cytochrome P-450 isoform 3A4. Certain drugs that have a significant inhibitory effect at therapeutic doses on this metabolic pathway can substantially raise the plasma levels of HMG-CoA reductase inhibitors and thus increase the risk of myopathy. These include cyclosporine, itraconazole, ketoconazole and other antifungal azoles, the macrolide antibiotics erythromycin, and clarithromycin, and the antidepressant nefazodone.

Reducing the risk of myopathy:

1. General measures.

Patients starting therapy with lovastatin should be advised of the risk of myopathy, and told to report promptly unexplained muscle pain, tenderness or weakness. A CPK level above 10X upper limit of normal in a patient with unexplained muscle symptoms indicates myopathy. Lovastatin therapy should be discontinued if myopathy is diagnosed or suspected. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CPK 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 lovastatin 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).

Physicians contemplating combined therapy with lovastatin and any of the interacting drugs should weigh the potential benefits and risks, and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent myopathy.

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

In patients taking concomitant cyclosporine, fibrates or niacin, the dose of lovastatin should generally not exceed 20 mg as the risk of myopathy increases substantially at higher doses (see **DOSAGE** and **ADMINISTRATION**, Concomitant Therapy). Interruption of lovastatin therapy during a course of treatment with a systemic antifungal azole or a macrolide antibiotic should be considered. Concomitant use with other medicines labeled as having a potent inhibitory effect on cytochrome P-450 3A4 at therapeutic doses should be avoided unless the benefits of combined therapy outweigh the increased risk.

Hepatic Effects:

In the initial controlled clinical trials performed in 695 patients, marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.6% of adult patients who received lovastatin for at least one year (see **ADVERSE REACTIONS** under Laboratory Tests). When the drug was interrupted or discontinued in these patients, the transaminase levels fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin. In most cases they were not associated with jaundice or other clinical signs or symptoms (see **PRECAUTIONS**, **DRUG INTERACTIONS** and **ADVERSE REACTIONS, POST MARKETING EXPERIENCE**).

In the 48-week EXCEL study performed in 8245 patients suffering from moderate hypercholesterolemia, the incidence of marked (more than 3 times the upper limit of normal) increases in serum transaminases on successive testing was 0.1% in patients receiving a placebo and 0.1% at 20 mg/day, 0.9% at 40 mg/day and 1.5% at 80 mg/day in patients administered lovastatin. A significant lovastatin dose-related trend was noted for confirmed serum transaminase elevation > 3 times the upper limit of normal (see **PHARMACOLOGY**, Clinical Studies).

It is recommended that liver function tests be performed at baseline and periodically thereafter in all patients. Particular attention should be paid to patients who develop elevated serum transaminase levels and in patients in whom the dose is increased to 40 mg/day or more. In these patients, measurements should be repeated promptly and then performed more frequently.

If the transaminase levels show evidence of progression, particularly if they rise to three times the upper limit of normal and are persistent, the drug should be discontinued.

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

serum transaminase elevations are contraindications to the use of lovastatin; if such condition develops during therapy, the drug should be discontinued.

Moderate elevations of serum transaminases (less than three times the upper limit of normal) have been reported following therapy with lovastatin (see **ADVERSE REACTIONS**). These changes were not specific to lovastatin and were also observed with comparative lipid metabolism regulators. They generally appeared within the first 3 months after initiation of therapy, were often transient and were not accompanied by any other symptoms. They did not necessitate interruption of treatment.

PRECAUTIONS

General:

Before instituting therapy with lovastatin tablets, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in overweight and obese patients, and to treat other underlying medical problems (see **INDICATIONS** and **CLINICAL USE**). The patient should be advised to inform subsequent physicians of the prior use of lovastatin or any other lipid metabolism regulator.

The effect of lovastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity or mortality or total mortality has not been established.

Use in Homozygous Familial Hypercholesterolemia (FH):

Lovastatin is not effective or is less effective in patients with rare homozygous familial hypercholesterolemia.

(For Heterozygous Familial Hypercholesterolemia (FH), see **PHARMACOLOGY**, Clinical Studies).

Patients with Severe Hypercholesterolemia:

Higher dosages (80 mg/day) required for some patients with severe hypercholesterolemia are associated with increased plasma levels of lovastatin. **Caution should be exercised in such patients who are also significantly renally impaired, elderly or are concomitantly administered P-450 inhibitors (see WARNINGS, Myopathy and PRECAUTIONS, Drug Interactions).**

Effect on the lens:

Current long-term data from clinical trials do not indicate an adverse effect of lovastatin on the human lens.

Effect on Lipoprotein(a) [Lp(a)]:

In some patients the beneficial effect of lowered total cholesterol and LDL-cholesterol levels may be partly blunted by a concomitant increase in the Lp(a) levels. Until further experience is obtained from controlled clinical trials, it is suggested, where feasible, that Lp(a) measurements be carried out in patients placed on therapy with lovastatin.

Effect on CoQ_{10} Levels (Ubiquinone):

A significant decrease in plasma CoQ_{10} levels in patients treated with lovastatin and other statins has been observed in short-term clinical trials. The clinical significance of a potential long-term statin-induced deficiency of CoQ_{10} has not yet been established (see **SELECTED BIBLIOGRAPHY**).

Hypersensitivity:

Although to date hypersensitivity syndrome has not been described as such, in few instances eosinophilia and skin eruptions appear to be associated with lovastatin treatment. If hypersensitivity is suspected, lovastatin should be discontinued.

Use in Obstetrics:

Lovastatin is contraindicated during pregnancy (see TOXICOLOGY, Teratogenicity and Reproductive Studies).

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

A few reports have been received of congenital anomalies in infants whose mothers were treated during a critical period of pregnancy with HMG-CoA reductase inhibitors including lovastatin (see **SELECTED BIBLIOGRAPHY**). In a review of approximately 100 prospectively followed pregnancies in women exposed to lovastatin or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. As safety in pregnant women has not been established and there is no apparent benefit to therapy with lovastatin during pregnancy, treatment should be immediately discontinued as soon as pregnancy is recognized.

Nursing Mothers:

It is not known whether lovastatin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in

nursing infants from lovastatin, women taking lovastatin should not nurse their infant (see **CONTRAINDICATIONS**).

Pediatric Use:

Limited experience is available in children. However, safety and effectiveness in children have not been established.

Geriatric Use:

In patients over 60 years, efficacy appeared similar to that seen in the population as a whole, with no apparent increase in the frequency of clinical or laboratory adverse findings.

Use in Patients with Impaired Renal Function:

Because lovastatin does not undergo significant renal excretion, modification of dosage should not be necessary in patients with moderate renal insufficiency.

In patients with severe renal insufficiency (creatinine clearance < 0.5 mL/s [30 mL/min]), dosages above 20 mg/day should be carefully considered and, if deemed necessary, implemented cautiously (see **PRECAUTIONS**, Muscle Effects, **PHARMACOLOGY**, Clinical Studies and **SELECTED BIBLIOGRAPHY**).

Endocrine Function:

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Clinical studies with lovastatin have shown that this agent does not reduce plasma cortisol concentration or impair adrenal reserve, and does not reduce basal plasma testosterone concentration. However, the effects of HMG-CoA reductase inhibitors on male fertility have not been studied in an adequate number of 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 be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g. ketoconazole, spironolactone, or cimetidine) that may decrease the levels of endogenous steroid hormones (see Drug Interactions, Cytochrome P-450 Inhibitors).

Drug Interactions

Concomitant Therapy with Other Lipid Metabolism Regulators:

Combined drug therapy should be approached with caution as information from controlled studies is limited.

Bile Acid Sequestrants:

Preliminary evidence suggests that the cholesterol-lowering effects of lovastatin and the bile acid sequestrant, cholestyramine, are additive.

When lovastatin is used concurrently with cholestyramine or any other resin, an interval of at least two hours should be maintained between the two drugs, since the absorption of lovastatin may be impaired by the resin.

Gemfibrozil, Fenofibrate and Niacin:

Myopathy, including rhabdomyolysis, has occurred in patients who were receiving coadministration of lovastatin with fibric acid derivatives and niacin, particularly in subjects with pre-existing renal insufficiency (see **WARNINGS**).

Erythromycin and Clarithromycin:

See **WARNINGS**, Muscle Effects.

Angiotensin-Converting Enzyme Inhibitors:

Hyperkalemia associated with myositis (myalgia and elevated CPK) has been reported in the case of a single patient with insulin-dependent diabetes mellitus and mild renal insufficiency who received lovastatin concomitantly with an angiotensin-converting enzyme inhibitor (lisinoprol).

Coumarin Anticoagulants:

Clinically evident bleeding and/or increased prothrombin time have been reported occasionally in 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 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.

Digoxin:

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

Beta-Adrenergic Blocking Drugs:

In healthy volunteers, the coadministration of propranolol and lovastatin resulted in a slight decrease of the AUC of lovastatin and its metabolites as well as in a significant decrease of the C_{max} for the lovastatin metabolites.

The clinical interpretation of this phenomenon is difficult as it may indicate a greater uptake of lovastatin by the liver.

There was no clinically relevant interaction reported in patients who have been receiving lovastatin concomitantly with beta-adrenergic blocking agents.

Antipyrine:

Antipyrine was used as a model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P-450 system). Lovastatin had no effect on the pharmacokinetics of antipyrine in hypercholesterolemic patients.

Cytochrome P-450 Inhibitors:

Lovastatin is metabolized by the microsomal hepatic system (cytochrome P-450 isoenzyme CYP 3A4). While lovastatin did not interact with antipyrine, it may interact with erythromycin, a known inhibitor of cytochrome P-450 isoform 3A4. Drugs or common agents such as grapefruit juice that inhibit this enzyme may represent a potential for drug interactions when combined with lovastatin. Caution should thus be exercised with concomitant use of drugs such as cyclosporine, antifungal agents (e.g. itraconazole, ketoconazole), macrolide antibiotics including erythromycin and clarithromycin, antidepressant (e.g. nefazodone) or grapefruit juice (see WARNINGS, Myopathy and **PRECAUTIONS**, Use in Patients with Impaired Renal Function, Endocrine Function and **SELECTED BIBLIOGRAPHY**).

Other Concomitant Therapy:

Although specific interaction studies were not performed, in clinical studies, lovastatin was used concomitantly with calcium-channel blockers (such as verapamil HCl, nifedipine and diltiazem HCl), a number of diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs), hypoglycemic drugs (chlorpropamide, glipizide, glyburide, insulin), without evidence to date of clinically significant adverse interactions.

Drug / Laboratory Test Interactions:

Lovastatin may elevate creatine phosphokinase and transaminase levels (see **ADVERSE REACTIONS**, Laboratory Tests). In the differential diagnosis of chest pain in a patient on therapy with lovastatin, cardiac and non-cardiac fractions of these enzymes should be determined.

ADVERSE REACTIONS

Lovastatin was compared to placebo in 8245 patients with hypercholesterolemia (total cholesterol 6.2 - 7.8 mmol/L) in a randomized, double-blind, parallel, 48-week expanded clinical evaluation of lovastatin (EXCEL study). Clinical adverse reactions reported as possible, probably or definitely drug-related in any treatment group are shown in the following table.

	PLACEBO (n=1663) %	LOVASTATIN 20 mg q.p.m. (n=1642) %	LOVASTATIN 40 mg q.p.m. (n=1645) %	LOVASTATIN 20 mg b.i.d. (n=1646) %	LOVASTATIN 40 mg b.i.d. (n=1649) %
Body as a Whole					
Asthenia	1.4	1.7	1.4	1.5	1.2
Gastrointestinal					
Abdominal pain	1.6	2.0	2.0	2.2	2.5
Constipation	1.9	2.0	3.2	3.2	3.5
Diarrhea	2.3	2.6	2.4	2.2	2.6
Dyspepsia	1.9	1.3	1.3	1.0	1.6
Flatulence	4.2	3.7	4.3	3.9	4.5
Nausea	2.5	1.9	2.5	2.2	2.2
Musculoskeletal					
Muscle cramps	0.5	0.6	0.8	1.1	1.0
Myalgia	1.7	2.6	1.8	2.2	3.0
Nervous System/ Psychiatric					
Dizziness	0.7	0.7	1.2	0.5	0.5
Headache	2.7	2.6	2.8	2.1	3.2
Skin					
Rash	0.7	0.8	1.0	1.2	1.3
Special Senses					
Blurred vision	0.8	1.1	0.9	0.9	1.2

Other clinical adverse reactions 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

No significant difference was found among the different treatment groups including placebo in the incidence of serious clinical adverse experiences including death due to CHD, nonfatal myocardial infarction, cancer, and deaths due to all causes. This study was not designed or powered to evaluate the incidence of these serious clinical adverse experiences. The EXCEL study included a minority of patients at risk of or with coronary artery disease; however, its findings cannot be extrapolated in this respect to other segments of the high-risk population.

Laboratory Tests:

Marked persistent increases of serum transaminases have been noted (see **WARNINGS**).

Other liver function test abnormalities including elevated alkaline phosphatase and bilirubin have been reported. In the EXCEL study, 7.3% of the patients on lovastatin had elevations of CPK levels of at least twice the normal value on one or more occasions compared to 6.2% on placebo.

The EXCEL study, however, excluded patients with factors known to be associated with an increased risk of myopathy (see **WARNINGS**, Muscle Effects and **PRECAUTIONS**, Drug / Laboratory Test Interactions).

Nervous System:

Visual evoked response, nerve conduction measurements and electromyography in over 30 patients showed no evidence of neurotoxic effects of lovastatin.

Effect on the lens:

(see **PRECAUTIONS**).

Post Marketing Experience:

The following additional side effects have been reported since the drug was marketed: hepatitis, cholestatic jaundice, vomiting, anorexia, paresthesia, peripheral neuropathy, psychic disturbances including anxiety, alopecia, erythema multiforme, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus-like syndrome, polymyalgia rheumatica, vasculitis, thrombocytopenia, leukopenia, eosinophilia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, flushing, chills, dyspnea and malaise.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

In the event of overdosage, treatment should be symptomatic and supportive, liver function should be monitored, and appropriate therapy instituted. Until further experience is obtained, no specific therapy for overdosage can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known.

DOSAGE AND ADMINISTRATION

The patient should be placed on at least an equivalent of the American Heart Association (AHA) Step 1 diet before receiving **RAN-LOVASTATIN** (lovastatin tablets) and should continue on this diet during treatment with lovastatin. If appropriate, a program of weight control and physical exercise should be implemented.

Patients with hypercholesterolemia:

The usual starting dose is 20 mg/day given as a single dose with the evening meal. Single daily doses given with the evening meal have been shown to be more effective than the same dose given with the morning meal, perhaps because cholesterol is synthesized mainly at night. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80 mg daily given in single doses or divided doses with the morning and evening meals (see **WARNINGS**, Myopathy and **PRECAUTIONS, DRUG INTERACTIONS**). Divided doses (i.e., twice daily) tend to be slightly more effective than single daily doses.

Patients with Severe Hypercholesterolemia:

In patients with severe hypercholesterolemia, higher doses (80 mg/day) may be required (see WARNINGS, Myopathy and **PRECAUTIONS**, **DRUG INTERACTIONS**).

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of lovastatin if cholesterol levels fall below the targeted range, such as that recommended by the Second Report of the U.S. National Cholesterol Education Program (NCEP) (See **SELECTED BIBLIOGRAPHY**).

Patients with Established Coronary Heart Disease:

In the trials involving patients with coronary heart disease and administered lovastatin with[X] (colestipol) or without[XX] concomitant therapy, the dosages used were 20 to 80 mg daily, given in single or divided doses. In the two trials which utilized lovastatin alone, the dose was reduced if total plasma cholesterol decreased to below 2.85 mmol/L or if LDL-cholesterol decreased to below 2.1 mmol/L, respectively.

Concomitant Therapy:

See **PRECAUTIONS**, Drug Interactions, Concomitant Therapy with Other Lipid Metabolism Regulators.

In patients taking cyclosporine, fibrate or niacin concomitantly with lovastatin, the maximum recommended dosage of **RAN-LOVASTATIN** is 20 mg/day (see **WARNINGS**, Muscle Effects).

X Familial Atherosclerosis Treatment Study (FATS)

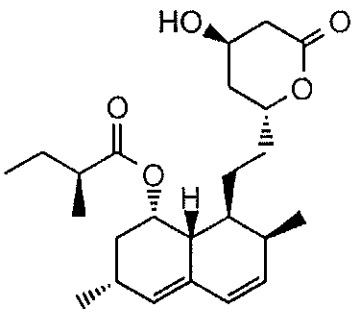
XX CCAIT, MARS Studies

PHARMACEUTICAL INFORMATION

Proper name: Lovastatin

Chemical name: Butanoic acid, 2-methyl-, 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 ester, [1*S*-[1α(*R**),3α, 7β,8β (2S*-4S*),8aβ]]-

Structural formula:



Molecular formula: $C_{24}H_{36}O_5$

Molecular weight: 404.55

Physical form: Lovastatin is a white to off-white crystalline powder.

Solubilities: Freely soluble in chloroform; soluble in acetone, in acetonitrile, and in methanol; sparingly soluble in alcohol; practically insoluble in hexane; insoluble in water.

Composition: **Each 20 mg tablet for oral administration contains:** 20 mg of lovastatin. **Non medicinal ingredients in alphabetical order:** Butylhydroxyanisole, FD&C Blue #2 lake, hydroxypropylcellulose, hydroxypropyl

methylcellulose, lactose anhydrous, magnesium stearate, microcrystalline cellulose, pregelatinized corn starch, talc and titanium dioxide.

Each 40 mg tablet for oral administration contains: 40 mg of lovastatin. **Non medicinal ingredients in alphabetical order:** Butylhydroxyanisole, D&C yellow #10 lake, FD&C blue #1 lake, hydroxypropylcellulose, hydroxypropyl methylcellulose, lactose anhydrous, magnesium stearate, microcrystalline cellulose, pregelatinized corn starch, talc and titanium dioxide.

Stability and storage Recommendations: Keep container tightly closed and store between 15-30°C. Protect from light.

AVAILABILITY OF DOSAGE FORMS

RAN-LOVASTATIN 20 mg tablet, a light blue coloured, octagon-shaped, biconvex film coated tablet, scored on one side, and "TEC" on the other side. Available in blister packages of 30 and in bottles of 100 and 500.

RAN-LOVASTATIN 40 mg tablet, is mint green coloured, octagon-shaped, biconvex film coated tablet, plain on one side, and "TEC" on the other side. Available in blister packages of 30 and in bottles of 100 tablets.

INFORMATION TO THE PATIENT

PrRAN-LOVASTATIN

Lovastatin tablets, MFR standard

20 mg and 40 mg

The Product Monograph is available only to the physician and pharmacist upon request.

RAN-LOVASTATIN is the brandname of AltiMed Pharma Inc., division of Technilab Pharma Inc., for the substance lovastatin available **only on prescription** from your physician. Lovastatin is one of a class of medicines known as **Lipid Metabolism Regulators**. They **inhibit**, in other words block, an enzyme that is necessary for the body to make cholesterol. In this way, less cholesterol is produced in the liver.

When it is necessary to lower cholesterol, physicians usually try to control the condition, known as hypercholesterolemia, with a carefully supervised diet. Also your physician may recommend other measures such as exercise and weight control. Medicines like this one are prescribed **along with,** and **not as a substitute for,** a special diet and other measures. Lovastatin is used to lower the levels of cholesterol (particularly Low Density Lipoprotein (LDL) cholesterol) and other fats in the blood. This may help prevent heart disease if caused by cholesterol clogging the blood vessels or slow the progression of atherosclerosis (hardening) of the arteries that nourish your heart, so-called coronary heart disease (CHD).

Remember - This medicine is prescribed for the particular condition that you have. **Do not give this medicine to other people, nor use it for any other condition.**

Do not use outdated medicine.

Store your tablets in a tightly closed container between 15-30°C, away from heat and direct light. Keep this product and all medicine out of the reach of children.

Read the following information carefully. **If you need any explanations, or further information, ask your physician or pharmacist.**

BEFORE TAKING THIS MEDICINE

This medicine may not be suitable for certain people. So, tell your physician if you think **any** of the following applies to you:

- You have previously taken lovastatin or any other medication in the same class - example, simvastatin, pravastatin, atorvastatin, fluvastatin or cerivastatin - and were allergic, or had reacted badly to it.

- You have liver disease.

- **You are pregnant or intend to become pregnant.** This medicine should **not** be used during pregnancy.

- You are breast-feeding or intend to breast-feed.

Your physician also needs to know if you are taking any other medication, whether on prescription or otherwise. It is particularly important to inform your physician if you are taking:

- Cyclosporine, gemfibrozil, lipid-lowering doses of niacin, corticosteroids, or an anticoagulant (e.g. drugs that prevent blood clots, such as warfarin, digoxin, erythromycin or clarithromycin, antifungal agents (itraconazole or ketoconazole) or nefazodone.

The safety of this medicine has not been established in adolescents and children.

PROPER USE OF THIS MEDICINE

- Take this medicine **exactly** as your physician ordered. It is usually recommended as a single dose with the evening meal or in two divided doses with the morning and evening meals.

- If you miss taking a tablet at its usual time, take it as soon as possible. But, if it is too close to the time of your next dose: take only the prescribed dose at the appointed time. **Do not take a double dose.**

- Carefully follow any measures that your physician has recommended for diet, exercise or weight control.

- It is important to continue taking the tablets as instructed. **Do not alter the dosage or stop taking the medicine without consulting your physician.**

- Keep your appointments regularly with your physician so that your blood can be tested and your progress checked at proper intervals.

- Avoid drinking large quantities of alcohol.

- **Do not start taking any other medicines** unless you have discussed the matter with your physician.

- Let your physician know if you suffer a severe injury, or severe infection.

- If you have to undergo any kind of surgery, tell your physician about the planned surgery; and also inform the dentist or the physician in charge that you are taking this or any other medicine.

SIDE EFFECTS OF THIS MEDICINE - AND WHAT YOU SHOULD DO:

Along with its intended action, any medication may cause unwanted effects. Most people do not have any problem when taking this medicine; but if you notice any of the following reactions, **check with your physician as soon as possible:**

- Aching muscles, muscle cramps, tiredness or weakness
- Fever
- Blurred vision

Some other side effects that may occur, generally do not require medical attention, and may come and go during treatment. But if any of the following persist or become troublesome, **do check with your physician or pharmacist:**

- Constipation, diarrhea, gas, stomach upset, nausea
- Pain in the abdomen
- Headache, dizziness
- Skin rash

Some people may have other reactions, If you notice **any unusual effect,** check with your physician or pharmacist.

INGREDIENTS:

Active ingredient: Each tablet of **RAN-LOVASTATIN** contains lovastatin. It comes in 2 strengths: 20 mg (light blue), and 40 mg (mint green).

RAN-LOVASTATIN 20 mg tablets: Non-medicinal ingredients in alphabetical order: Butylhydroxyanisole, FD&C Blue #2 lake, hydroxypropylcellulose, hydroxypropyl methylcellulose, lactose anhydrous, magnesium stearate, microcrystalline cellulose, pregelatinized corn starch, talc and titanium dioxide.

RAN-LOVASTATIN 40 mg tablets: Non-medicinal ingredients in alphabetical order: Butylhydroxyanisole, D&C yellow #10 lake, FD&C blue #1 lake, hydroxypropylcellulose, hydroxypropyl methylcellulose, lactose anhydrous, magnesium stearate, microcrystalline cellulose, pregelatinized corn starch, talc and titanium dioxide.

PHARMACOLOGY

Human pharmacology:

Lovastatin has been shown to reduce both normal and elevated LDL cholesterol concentrations **The effect of lovastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity or mortality, as well as on total mortality, has not been established.**

LDL is formed from VLDL and is catabolized predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of lovastatin may involve both reduction of VLDL-cholesterol concentration, and induction of the LDL receptor leading to reduced production and/or increased catabolism of LDL-cholesterol.

Apolipoprotein B also falls substantially during treatment with lovastatin. Since each LDL particle contains one molecule of apolipoprotein B, and since little apolipoprotein B is found in other lipoproteins, this strongly suggests that lovastatin does not merely cause cholesterol to be lost from LDL, but also reduces the concentration of circulating LDL particles. However, a change in the composition of the LDL particle (lipid/protein ratio) cannot be excluded during treatment with lovastatin. In addition, lovastatin slightly increases HDL-cholesterol and reduces VLDL-cholesterol and plasma triglycerides (see Tables I-IV under Clinical Studies).

The active form of lovastatin is a specific reversible inhibitor of HMG-CoA reductase, the enzyme which catalyzes the conversion of HMG-CoA to mevalonate. However, at therapeutic doses, the enzyme is not completely blocked, thereby allowing biologically necessary amounts of mevalonate to be available. Because the conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol, therapy

with lovastatin would not be expected to cause an accumulation of potentially toxic sterols.

Although cholesterol is the precursor of all steroid hormones, lovastatin, at therapeutic doses, has been shown to have no effect on steroidogenesis (see **PRECAUTIONS**, Endocrine Function).

Pharmacokinetics:

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

Following an oral dose of ^{14}C-labeled lovastatin to 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. As a consequence of extensive hepatic extraction of lovastatin, the availability of drug to the general circulation is low and variable. In a single dose study in four hypercholesterolemic patients, it was estimated that less than 5% of an oral dose of lovastatin reaches the general circulation as active inhibitors. Following administration of lovastatin tablets the coefficient of variation, based on between-subject variability, was approximately 40% for the area under the curve of total inhibitory activity in the general circulation.

Both lovastatin and its β-hydroxy acid metabolite are highly bound (>95%) to human plasma proteins. Animal studies demonstrated that lovastatin crosses the blood-brain and placental barriers.

Lovastatin is metabolized by the microsomal hepatic enzyme system (cytochrome P-450 isoform 3A4). The major active metabolites present in human plasma are the β-hydroxy acid of lovastatin, its 6'-hydroxy, 6'-hydroxymethyl, and 6'-exomethylene

derivatives. Peak plasma concentrations of both active and total inhibitors were attained within 2 to 4 hours of dose administration. While the recommended therapeutic dose range is 20 to 80 mg/day, linearity of inhibitory activity in the general circulation was established by a single-dose study employing lovastatin tablet dosages from 60 to as high as 120 mg. With a once-a-day dosing regimen, plasma concentrations of total inhibitors over a dosing interval achieved a steady state between the second and third days of therapy and were about 1.5 times those following a single dose. When lovastatin was given under fasting conditions, plasma concentrations of both active and total inhibitors were on average about two-thirds those found when lovastatin was administered immediately after a standard test meal.

In a study of patients with severe renal insufficiency (creatinine clearance 0.167-0.5 mL/s [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.

Clinical Studies:

Lovastatin has been shown to be highly effective in reducing total and LDL-cholesterol in heterozygous familial and non-familial forms of 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. When therapy with lovastatin is stopped, total cholesterol has been shown to return to pre-treatment levels.

In patients with heterozygous FH optimal reduction in total and LDL cholesterol necessitates a combination drug therapy in the majority of patients (see **SELECTED BIBLIOGRAPHY**) (For homozygous FH see **PRECAUTIONS**, Use in Homozygous Familial Hypercholesterolemia).

In multicenter, double-blind studies in over 200 patients with familial or non-familial hypercholesterolemia, lovastatin, administered in doses ranging from 20 mg q.p.m. to 40 mg b.i.d., was compared to placebo. Lovastatin consistently and significantly decreased total plasma cholesterol (TOTAL-C), LDL-cholesterol (LDL-C), total cholesterol/HDL-cholesterol (TOTAL-C/HDL-C) ratio and LDL-cholesterol/HDL-cholesterol (LDL-C/HDL-C) ratio ($p < 0.01$). In addition, lovastatin increased total HDL-cholesterol (HDL-C) and decreased VLDL-cholesterol (VLDL-C) and plasma triglycerides (TRIG.) (see TABLES I and II for dose response results).

TABLE I

FH STUDY

DOSE RESPONSE OF LOVASTATIN

(Percent change from baseline after 6 weeks)

DOSAGE	N	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	TRIG. (median)
Placebo	21	-1	-2	+1	-1	0	+3
LOVASTATIN							
20 mg q.p.m.	20	-18	-19	+10	-26	-24	-7
40 mg q.p.m.	21	-24	-27	+10	-32	-29	-22
10 mg b.i.d.	18	-22	-25	+6	-28	-25	-11
20 mg b.i.d.	19	-27	-31	+12	-38	-34	-18
40 mg b.i.d.	20	-34	-39	+8	-43	-38	-12

TABLE II

NON-FH STUDY

DOSE RESPONSE OF LOVASTATIN

(Percent change from baseline after 6 weeks)

DOSAGE	N	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	VLDL-C (median)	TRIG. (median)
Placebo	20	+5	+9	+4	+7	+3	-14†	-3
LOVASTATIN								
20 mg q.p.m.	19	-18	-22	+11	-29	-24	-30††	-17
40 mg q.p.m.	20	-19	-21	+4	-20	-19	-31†	-20
10 mg b.i.d.	19	-18	-24	+3	-25	-20	-2††	-15
20 mg b.i.d.	17	-29	-34	+6	-36	-31	-31†	-23
40 mg b.i.d.	20	-32	-39	+13	-46	-39	-31††	-27

† N = 17

†† N = 18

Lovastatin was compared to cholestyramine in an open parallel study in patients with hypercholesterolemia who were at high risk of myocardial infarction. At all dosage levels, lovastatin produced a significantly greater reduction of total plasma cholesterol, LDL-cholesterol, VLDL-cholesterol, triglycerides, and total cholesterol/HDL-cholesterol ratio when compared to cholestyramine. The increases in HDL-cholesterol achieved with lovastatin and cholestyramine were similar (see Table III).

TABLE III

LOVASTATIN vs Cholestyramine

(Percent change from baseline after 12 weeks)

DOSAGE	N	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	VLDL-C (median)	TRIG. (median)
Lovastatin								
20 mg b.i.d.	85	-27	-32	+9	-36	-31	-34	-21
40 mg b.i.d.	88	-34	-42	+8	-44	-37	-31	-27
Cholestyramine								
12 g b.i.d.	88	-17	-23	+8	-27	-21	+2	+11

An expanded clinical evaluation of lovastatin (EXCEL study) was performed comparing lovastatin to placebo in 8245 patients with hypercholesterolemia, total cholesterol 6.2-7.8 mmol/L and LDL cholesterol >4.1 mmol/L. This was a randomized, double-blind, parallel study, which extended over 48 weeks. The patient population was selected with or without other risk factors and with or without evidence of coronary disease. Lovastatin was the sole hypolipidemic agent used in virtually all patients in this study. Total, LDL- and HDL-cholesterol and triglycerides were measured. All changes in plasma levels were dose-related, similar to those shown in the initial clinical trials, and significantly different from those with placebo ($\leq$0.001) (Table IV).

TABLE IV

LOVASTATIN vs Placebo

(Percent change from baseline -

Average values between weeks 12 and 48)

DOSAGE	N*	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	TRIG. (median)
Placebo	1663	+0.7	+0.4	+2.0	+0.2	+0.6	+4
LOVASTATIN							
20 mg**	1642	-17	-24	+6.6	-27	-21	-10
40 mg**	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

** With evening meal

The effect of treatment with lovastatin on coronary atherosclerosis was evaluated in three randomized, double-blind, placebo-controlled trials of 2 - 2 ½ years' duration. All patients had coronary atherosclerosis on angiograms evaluated by computerized quantitative coronary angiography (QCA).

In the first trial[1], the effect of lovastatin 20 to 80 mg daily was studied in 331 patients with serum total cholesterol 5.70 - 7.77 mmol/L. Lovastatin significantly slowed the progression of lesions and decreased the number of patients with new lesions. This effect was not accompanied by an improvement in the clinical endpoints (death, fatal/non fatal myocardial infarction, hospitalization for unstable angina, and coronary revascularization procedures) within the two years' duration of treatment (see **INDICATIONS** and **CLINICAL USE**).

In the second trial[2], the effect of treatment with lovastatin 40 mg b.i.d. was studied in 270 patients with serum total cholesterol 4.92 - 7.64 mmol/L. By QCA, there was no statistically significant difference between groups in change of percent stenosis for all lesions (the primary endpoint). However, angiograms were also evaluated by expert angiographers who formed a consensus opinion of overall angiographic change - the Global Change Score (a secondary endpoint). By this method, it was shown that lovastatin significantly slowed the progression of disease overall and doubled the number of patients who showed regression of lesions. No difference in clinical events were detected during the 2.2 years of double-blind therapy (see **INDICATIONS** and **CLINICAL USE**).

The trials described above were not designed or powered to demonstrate a reduction in the risk of coronary morbidity and mortality as well as total mortality.

In the third trial[3], the effect of combined therapy with lovastatin and colestipol was studied in 98 patients with a family history of premature vascular disease, apolipoprotein B levels $\geq$ 1.3 g/L and an average total cholesterol of 6.99 mmol/L. Lovastatin and colestipol significantly reduced the frequency of progression and increased the frequency of regression of coronary lesions.

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1 Canadian Coronary Atherosclerosis Intervention Trial (CCAIT)

2 Monitored Atherosclerosis Regression Study (MARS)

3 Familial Atherosclerosis Treatment Study (FATS)

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 Plaque Study (ACAPS), the effect of therapy with lovastatin on carotid atherosclerosis was assessed by B-mode ultrasonography in patients with early, asymptomatic carotid lesions, with mean serum total cholesterol of 6.1 mmol/L (235 mg/dL) 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. 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 (5 vs 14, $p = 0.04$) and a significant reduction in all-cause mortality (1 vs 8, $p = 0.02$) relative to the placebo group. This trial should be viewed as supportive and complementary to the others mentioned above. However, it was not powered to demonstrate a reduction in the risk of coronary morbidity and mortality. A larger trial of longer duration is needed to clarify the effect of lovastatin in monotherapy on clinical events (see **WARNINGS, INDICATIONS** and **CLINICAL USE** and **SELECTED BIBLIOGRAPHY**).

Lovastatin has been shown to be effective in uncomplicated, well controlled insulin dependent (Type 1) and non-insulin dependent (Type 2) diabetic patients with primary hypercholesterolemia. Reductions of plasma lipids were comparable to that reported in non-diabetic patients. Glucose control was not adversely affected.

In one controlled study in elderly patients over the age of 60, efficacy appeared similar to that seen in the population as a whole, and there was no apparent increase in the frequency of clinical or laboratory adverse findings.

Animal Pharmacology:

Cell culture: Lovastatin is a potent reversible inhibitor of sterol synthesis from ^{14}C-acetate in cell cultures.

Two established cell lines, a mouse fibroblast line (L-M cells) and a rat liver cell line (GAI cells) were used.

In these cells it was found that lovastatin is a potent inhibitor of sterol synthesis from ^{14}C-acetate with IC_{50} values of 11.1 and 2.7 nM respectively. The incorporation of ^{3}H-mevalonate, the product of the HMG-CoA reductase reaction into sterols, was not affected in either cell line while incorporation of ^{14}C-acetate into fatty acids was slightly stimulated. These results demonstrate that lovastatin does not inhibit the enzymes of cholesterol biosynthesis after the formation of mevalonate nor does it inhibit the enzymes required for the biosynthesis of fatty acids.

In the HMG-CoA reductase assay, lovastatin (a lactone) was 75 times less active than its corresponding open hydroxy acid (to which it is converted after oral ingestion in man).

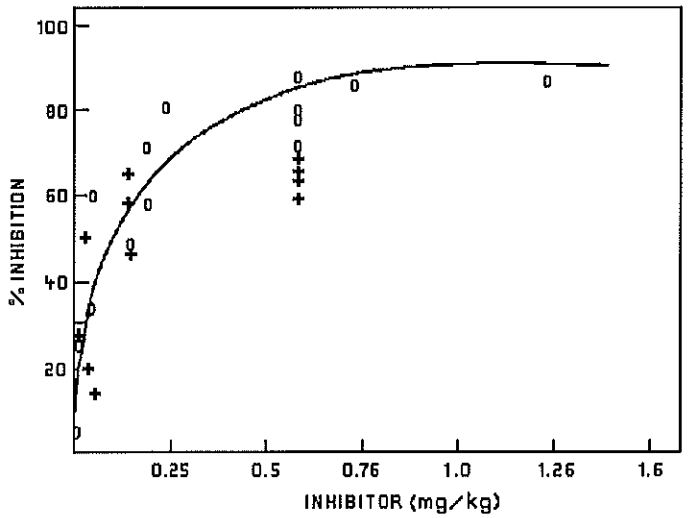
Rats:

Lovastatin and its open acid form metabolite were administered to male rats (10/group) at doses of 0.01 to 1.25 mg/kg. The open acid was more active in inhibiting cholesterol synthesis from acetate (see Figure 1).

Figure 1

Effect of lovastatin (+) and the open acid form (0) on cholesterol synthesis in the rat (n=10 for each point).

Inhibitor (mg/kg)



In male rats (n = 10/group), administration of lovastatin in the diet at concentrations of 0.003 to 0.075%, for 7 days, resulted in an 8-51% decrease in total serum cholesterol as seen in TABLE V.

TABLE V

Plasma cholesterol lowering in rats; percent inhibition as a function of percent dietary Lovastatin

Lovastatin[a] (% in diet)	Serum cholesterol (% Lowering from control) Total	LDL + VLDL	HDL
0.00312	8	8	8
0.00625	12	16	9
0.0125	29	45	17
0.025	28	50	13
0.05	45	74	24
0.075	51	78	32

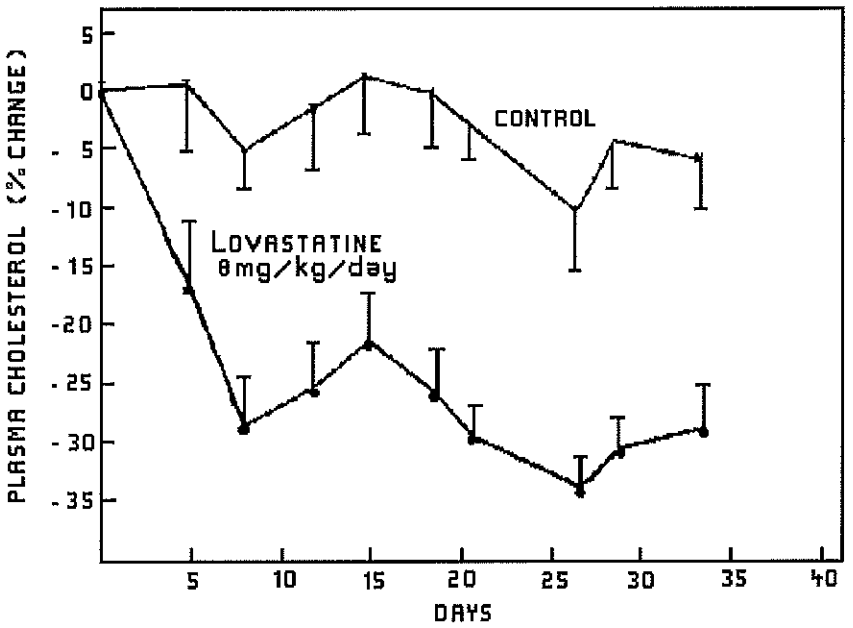
[a]Rats (n=10/group) treated for 7 days with indicated levels of lovastatin. Animals maintained on a reverse lighting schedule (lights off at 4.00 a.m. and on at 4:00 p.m.). Assays were carried out 5-6 hours into lights out cycle.

Dogs:

Eight dogs received 8 mg/kg/day, p.o. of lovastatin in their diet for a period of 34 days and 4 dogs served as controls. The maximum decrease was obtained by Day 8 of treatment and remained relatively constant for the remainder of the experiment. Decreases in plasma cholesterol ranged from 18.3% to 42.1% (mean 27.6 ± S.E. of 2.8%). The results of this study are illustrated in Figure 2.

Figure 2

Effect of lovastatin on plasma cholesterol levels in dogs



Dogs were responsive to the plasma cholesterol-lowering effects of lovastatin and its open hydroxy acid, particularly if the animals were given cholestyramine concomitantly.

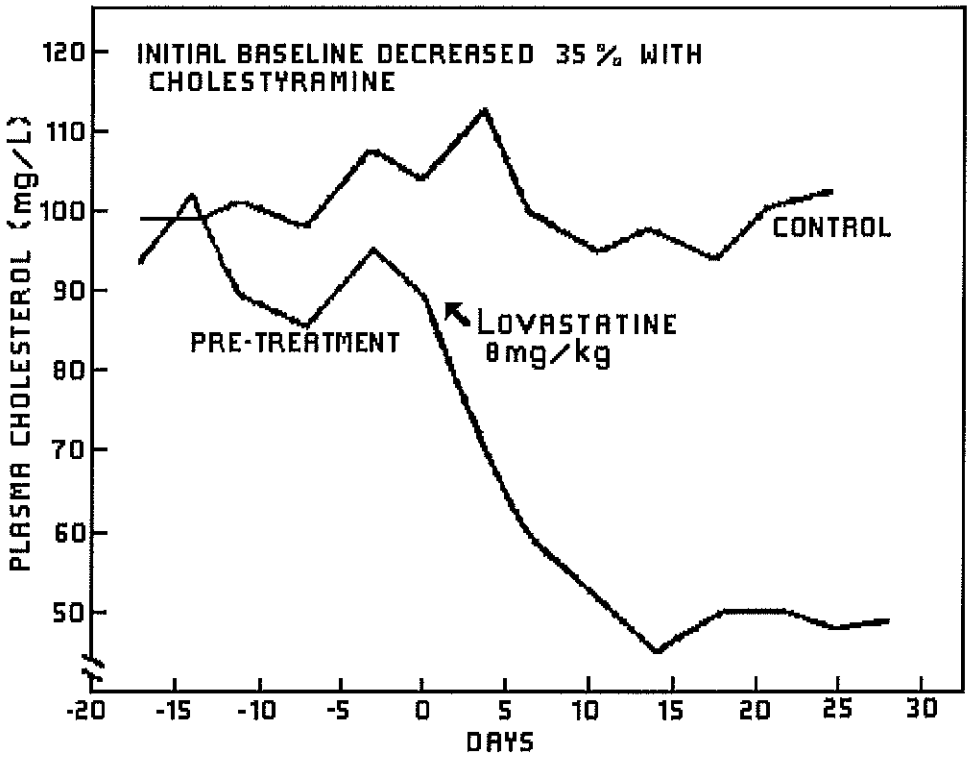
In four male beagle dogs, cholestyramine, a bile acid sequestrant, administered at a dose of 12 g/day resulted in an average sustained reduction in total plasma cholesterol of approximately 35%.

Two of these dogs later received 8 mg/kg/day of lovastatin. In the treated animals, there was a rapid response to treatment with cholesterol levels decreasing from an

average value of 2.39 mmol/L (92.4 mg/dL) prior to treatment to 1.20 mmol/L (46.5 mg/dL) after treatment. The results of this study are illustrated in Figure 3.

Figure 3

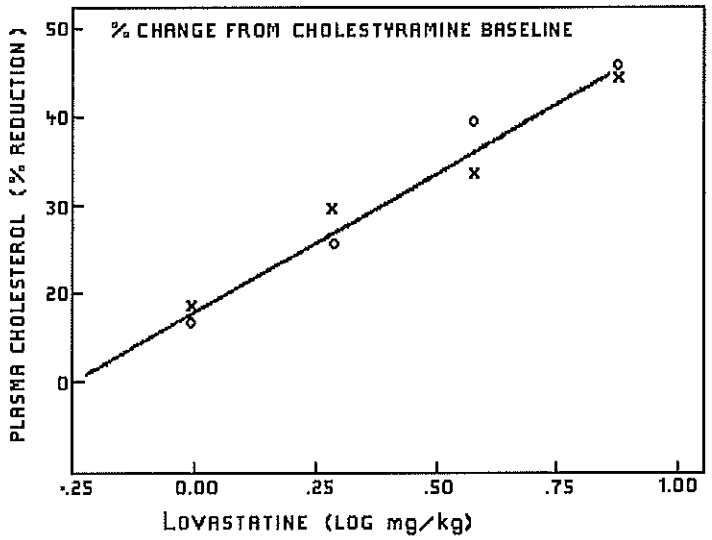
Plasma cholesterol lowering following oral administration of 8 mg/kg/day lovastatin in cholestyramine treated dogs (n=2).



Addition of lovastatin to the diet of cholestyramine primed dogs at levels of 1 to 8 mg/kg/day (2 dogs/dose group) resulted in a further dose-dependent decrease in plasma cholesterol of 14.2% (at 1 mg/kg/day) to 49.3% (at 8 mg/kg/day) below the levels established with cholestyramine alone. Withdrawal of lovastatin led to a gradual increase in plasma cholesterol levels to the original cholestyramine-induced values. Under these conditions there was a log-dose response as shown in Figure 4.

Figure 4

Plasma cholesterol lowering in cholestyramine-treated dogs as function of log of dose per day (n=2). X, % reduction based on pretreatment baseline; 0, % reduction based on recovery baseline after cessation of treatment.



In the cholestyramine-primed dog model, the open acid metabolite was 2-4 times more potent than lovastatin as a plasma cholesterol-lowering agent.

Rabbits:

Rabbits become hypercholesterolemic when they are fed cholesterol-free semi-synthetic diets which contain casein.

Four male hypercholesterolemic rabbits received lovastatin at a dose of 6 mg/kg/day, p.o. (administered by stomach tube) for a period of 21 days and four other hypercholesterolemic rabbits served as controls. Cholesterol levels of treated rabbits decreased by an average of 61.2 (± 11.0) % compared to 13.6% for the control rabbits. LDL decreased markedly and HDL remained constant or increased.

Lovastatin administered at a dose of 20 mg/animal/day, p.o., (4 rabbits/group) prevents the increase of LDL-cholesterol in rabbits fed with a casein diet.

This effect is shown to be mediated through regulation of the levels of hepatic LDL-binding sites and increase in the rate of catabolism of LDL by the liver.

Pharmacokinetics:

The pharmacokinetic profile of lovastatin has been investigated in mice, rats, dogs and monkeys. About 30% of an oral dose is absorbed and lovastatin is rapidly hydrolysed, probably in the plasma and in the liver, to an active open hydroxy acid metabolite. In the dog the availability of the absorbed drug to the general circulation is limited by its extensive first-pass extraction in the liver, probably its primary site of action, with subsequent excretion of drug equivalents in the bile. The major pharmacokinetic parameters in the animals are presented in Table VI.

TABLE VI

Pharmacokinetic parameters in animals

		INTRAVENOUS		ORAL		
		DOSE	AUC	DOSE	Tmax	AUC
MOUSE	Lovastatin	0.6	0.38	50	2	8.65
RAT	Lovastatin	0.8	0.776	8	2	1.91
	Open hydroxy acide metabolite	5	10.4	5	0.5	5.5
DOG	Lovastatin	0.8	1.64	8	2	1.4
	Open hydroxy acid metabolite	5	17.5	5	0.25	16.4
MONKEY	Lovastatin	0.8	1.17	8	2	0.82
	Open hydroxy acid metabolite	5	5.9	5	1	4.1

Doses are expressed in mg/kg.

AUC values are in $\mu gEq \cdot hr \cdot mL^{-1}$ and are for $0 \rightarrow 24$ hr.

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, the primary site of action, with subsequent excretion of drug in the bile.

In all species studied, lovastatin and its active metabolite are >95% bound to plasma albumin.

The apparent volumes of distribution of lovastatin administered p.o. are 5 L/kg, 4 L/kg and 10 L/kg in rats, dogs and monkeys respectively. The apparent volumes of distribution of the open hydroxy acid metabolite administered intravenously are 2, 0.5 and 18 L/kg in rats, dogs and monkeys respectively.

About 90% of an oral dose of lovastatin is recovered in the feces and less than 2% in the urine.

TOXICOLOGY

Acute Toxicity

TABLE VII

Lovastatin			
Species	**Sex**	**Route**	**LD_{50} mg/kg (95% confidence limits)**
Rat	Female	Oral	> 5000
Rat	Male	Oral	> 5000
Mouse	Female	Oral	> 20000
Mouse	Male	Oral	> 20000
Open Hydroxy Acid Form of Lovastatin L-154,819			
Species	**Sex**	**Route**	**LD_{50} mg/kg (95% confidence limits)**
Mouse	Female	Oral	1230-1380
Mouse	Male	Oral	1230-1380
Mouse	Female	Intravenous	272-287
Mouse	Male	Intravenous	272-287
Rat	Female	Oral	$\simeq$ 1260
Rat	Male	Oral	$\simeq$ 1260
Rat	Female	Intraperitoneal	$\simeq$ 113
Rat	Male	Intraperitoneal	$\simeq$ 113

Subacute and Chronic Toxicity Studies

The spectrum of effects produced by lovastatin in mice, rats, rabbits, dogs and monkeys shown on Table VIII is not unexpected in view of the magnitude of the dosage levels employed and the potency of lovastatin against the HMG-CoA reductase.

TABLE VIII

Lovastatin:

Target organs observed in animal studies

Organ	Mouse	Rat	Rabbit	Dog	Monkey
Liver, neoplastic effect	+	-	-	-	-
Liver, non-neoplastic effect	+	+	+	+	-
Kidney	-	-	+	-	-
Gallbladder	-	NA	+	-	-
Stomach (non-glandular)	+	+	NA	NA	NA
Fetus	+	+	-	NT	NT
Eye (lens)	-	-	-	+	-
Brain (vasculature, optic tract)	-	-	-	+	-
Testes	-	-	-	+	-

\+ = Organ affected in some way by drug treatment

\- = No effect observed in this organ in this species

NT = Not tested

NA = Not applicable (organ does not exist in this species)

The following table summarizes the significant adverse changes noticed during the long-term toxicology studies with lovastatin.

TABLE IX

Lovastatin

Significant adverse changes

	MINIMAL TOXIC DOSE (mg/kg/day)	NO-EFFECT DOSE (mg/kg/day)
MICE		
Hepatic tumors	500	100
Non-glandular gastric mucosa		
• Acanthosis	100	20
• Papillomas	100	20
Pulmonary adenoma	500	100
RATS		
Morphologic abnormalities in liver		
• Foci of cellular alteration	30	5
• Cellular atypia	30	5
Teratology		
• Skeletal malformations	800	80
Non-glandular gastric mucosa		
• Acanthosis, hyperkeratosis, submucosal edema	200	180
Elevated serum transaminase activity	30	5
RABBITS		
Hepatocellular necrosis	100	25
Renal tubular necrosis	100	25
DOGS		
Death	180	60
CNS pathology		
• Vascular degeneration (with associated focal hemorrhage and perivascular edema)	180	60
• Optic tract degeneration	60	30
Cataracts	60	30
Testicular degeneration	20	5
Elevated serum transaminase activity	20	5

An extensive series of studies were performed with the specific intent of exploring the relationship between the adverse changes and inhibition of HMG CoA-reductase with the goal of providing the necessary perspective for human risk assessment.

The results of these studies are shown on the table below:

TABLE X

Lovastatin:

Key issues Identified in Safety Assessment –

Relationship to inhibition of HMG-CoA Reductase

Clearly Mechanism-Based

- Hepatic morphologic changes in rats
- Hepatic necrosis in rabbits
- Teratology in rats
- Hyperplasia of gastric non-glandular mucosa in rodents

Most Probably Mechanism-Based

- Cataracts in dogs
- Papillomas in non-glandular gastric mucosa in mice
- Elevated serum transaminase activity in rats and dogs
- Renal tubular necrosis in rabbits

Relationship to Mechanism of Action Unknown; Possibly Mechanism-Based

- Associated with marked lowering of serum lipids
  - Vascular and neuronal degeneration in CNS of dogs
- Not associated with marked lowering of serum lipids
  - Liver tumors in mice
  - Testicular degeneration in dogs

Carcinogenesis and Mutagenesis Studies:

In a 21-month carcinogenic study in mice, a statistically significant ($p \leq 0.05$) increase in the incidence of spontaneous hepatocellular carcinomas and adenomas was observed at doses of 500 mg/kg/day of lovastatin (312 times the maximum recommended human dose). These changes were not seen in mice given doses of 20 and 100 mg/kg/day (12.5 and 62.5 times the maximum recommended human dose).

A statistically significant increase ($p \leq 0.05$) in the spontaneous incidence of pulmonary adenomas was seen in female mice receiving 500 mg/kg/day (312 times the maximum recommended human dose); no similar changes were seen in males at any dose or in females receiving 20 or 100 mg/kg/day (12.5 or 62.5 times the maximum recommended human dose). Because the incidence of pulmonary tumors was within the range of untreated animals in studies of similar duration, the relationship of this latter change to treatment is not known.

In addition, an increase in the incidence of papilloma in the non-glandular mucosa of the stomach was observed in mice receiving 100 and 500 mg/kg/day (62.5 and 312 times the maximum recommended human dose); no increase was seen at a dosage of 20 mg/kg/day (12.5 times the maximum recommended human dose). The glandular mucosa was not affected. The human stomach contains only glandular mucosa. Importantly, there is a strong association between this change and hyperplasia of the squamous epithelium (acanthosis) in this region; acanthosis is a characteristic change observed in the non-glandular mucosa of rodents treated with HMG-CoA reductase inhibitors and is most probably a result of inhibition of the reductase in this tissue.

Similar squamous epithelium is found in the esophagus and ano-rectal junction of the mouse, rat, dog and monkey; however, no evidence of a similar drug-induced hyperplastic response was observed in these tissues in studies of up to 21 months in the mouse given up to 500 mg/kg/day (312 times the maximum recommended human

dose), or in a study of 24 months in the rat given 180 mg/kg/day (112 times the maximum recommended human dose).

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

Teratogenicity and Reproductive Studies:

Lovastatin has been shown to produce skeletal malformations in the rat fetus at doses of 800 mg/kg/day (500 times the maximum recommended human dose). At similar doses in mice, an increase in skeletal malformations was observed. These individual changes are within the range observed spontaneously in this strain of mouse. No drug-induced changes were seen in either species at doses of up to 80 mg/kg/day (50 times the maximum recommended human dose). No evidence of malformations was noted in rabbits at up to 15 mg/kg/day (the highest tolerated dose and about 9 times the maximum recommended human dose).

No drug-related effects on fertility were found in studies with rats. Lovastatin is excreted in rat milk.

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