PRODUCT MONOGRAPH

Nu-Lovastatin

(Lovastatin Tablets USP)

20mg and 40 mg

Lipid Metabolism Regulator

Nu-Pharm Inc.
50 Mural Street, Units 1&2
Richmond Hill, Ontario
L4B 1E4

Date of Preparation

1999.06.24

Control #061937

PRODUCT MONOGRAPH

NU-LOVASTATIN

(Lovastatin) Tablets USP

20 mg and 40 mg

THERAPEUTIC CLASSIFICATION

Lipid Metabolism Regulator

ACTIONS AND CLINICAL PHARMACOLOGY

Lovastatin is a cholesterol-lowering agent isolated from a strain of *Coniothyrium fuckelli*. After oral ingestion, lovastatin, which is an inactive lactone, is hydrolyzed to the corresponding ß-hydroxyacid 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). The drug undergoes extensive and complex metabolism. The parent drug and its metabolites are eliminated mainly in the bile. The primary routes of biotransformation in humans include hydrolysis of the lactone ring to yield the pharmacologically active hydroxy acid, and the cytochrome P-450 mediated oxidation at the 6'-position of the fused-ring system to

form 6'-hydroxyl, 6'-hydroxymethyl and 6'-exomethylene derivatives. The cytochrome P-450 3A isoenzymes are primarily responsible for hydroxylation and dehydrogenation reactions of lovastatin.

COMPARATIVE EFFICACY STUDY

A randomized, double-blind, controlled, parallel study was performed to assess the relative efficacy of NU-LOVASTATIN versus Mevacor® in subjects with moderate primary hypercholesterolemia. The total cholesterol was measured and LDL-cholesterol levels of each subject were calculated and compared to baseline during a 6 week treatment period of lovastatin 20 mg/day as either NU-LOVASTATIN or Mevacor® 20 mg tablets. The results are summarized as follows:

Mean Maximal % Decrease from Baseline (CV)			
	NU-LOVASTATIN	Mevacor®	Relative Mean*
Total Cholesterol	25.4 (25)	25.8 (28)	94.0
LDL-Cholesterol	35.5 (24)	35.2 (21)	96.2

*Based on the least squares estimate of the geometric means.

Mean AUC of the Profile of % Decrease (CV)			
	NU-LOVASTATIN	Mevacor®	Relative Mean*
Total Cholesterol	104 (31)	100 (33)	97.8
LDL-Cholesterol	149 (28)	141 (28)	101.0

*Based on the least squares estimate of the geometric means.

INDICATIONS AND CLINICAL USE

NU-LOVASTATIN (lovastatin) 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 equations:

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.

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 patient‡, 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

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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: 148-156.

† DeLong DM, et al. A comparison of methods. JAMA 1986; 256: 2372-2377.

‡ Canadian Coronary Atherosclerosis Intervention Trial (CCAIT) Monitored Atherosclerosis Regression Study (MARS)

endpoints (death, fatal/nonfatal myocardial infarction, hospitalization for unstable angina, and coronary revascularization procedure [PTCA and CABG] within the 2 - 2½ years' 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).

CONTRAINDICATIONS

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

** The Asymptomatic Carotid Artery Progression Study (ACAPS)

WARNINGS

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.

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 WARNINGS, Muscle effects and PRECAUTIONS, Drug Interactions and Cytochrome P-450 Inhibitors).

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 Drug Interactions under PRECAUTIONS and Post Marketing Experience under ADVERSE REACTIONS).

In a 48-week expanded clinical evaluation of lovastatin (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 ULN (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 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 conditions develop 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.

MUSCLE EFFECTS

CPK: Transient elevations of creatine phosphokinase (CPK) levels are commonly seen in lovastatin-treated patients, but have usually been of no clinical significance.

Myalgia and muscle cramps have also been associated with lovastatin therapy.

Myopathy has occurred rarely and should be considered in any patient with diffuse myalgias, muscle tenderness or weakness and/or marked elevation of creatine phosphokinase (10 times the upper limit of normal). There have been reports of severe rhabdomyolysis

that precipitated acute renal failure. Therapy with lovastatin should be discontinued if marked elevation of CPK levels occurs, or if myopathy is diagnosed or suspected.

In the EXCEL study comparing lovastatin to placebo in 8245 patients, myopathy (defined as a CPK elevation > 10 times the ULN with associated muscle symptoms) occurred in one patient in the lovastatin 40 mg/day group (0.1%) and in four patients in the 80 mg/day group (0.2%).

The EXCEL study, however, excluded patients with factors known to be associated with an increased risk of myopathy, including rhabdomyolysis.

These factors include pre-existing renal insufficiency (usually as a consequence of long-standing diabetes), concomitant therapy with cyclosporine, gemfibrozil, or lipid-lowering doses of niacin, and erythromycin (see Drug Interactions and PHARMACOLOGY, Clinical Studies).

Lovastatin is metabolized by the cytochrome P-450 isoform 3A4. Cyclosporine, macrolide antibiotics (e.g. erythromycin, clarithromycin and azithromycin), and azole derivative antifungal agents (e.g. ketoconazole and itraconazole) are inhibitors of the cytochrome P-450 isoform 3A4. Concomitant administration of lovastatin with these agents could result in a significant increase in plasma concentrations of lovastatin and lovastatin acid, and an increased risk of skeletal muscle toxicity. (See PRECAUTIONS, Drug Interactions and Cytochrome P-450 Inhibitors).

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin.

In the initial clinical trials, about 30% of patients on immunosuppressive therapy, including cyclosporine, developed myopathy within a year after starting therapy with lovastatin. The corresponding incidence figures for concomitant therapy with

gemfibrozil and niacin were approximately 5% and 2% respectively. Most of these patients were taking lovastatin 40-80 mg/day. In seven subsequent reports, 148 cyclosporine-treated transplant patients (105 cardiac and 43 renal) received concurrent lovastatin 10-60 mg/day (the vast majority receiving 20 mg/day) for periods of 3 to 41 months with one reported case of rhabdomyolysis (0.6%) and one case of significant CPK elevations.

Therefore, the benefits and risks of using NU-LOVASTATIN concomitantly with immunosuppressive drugs, erythromycin, fibrates or lipid-lowering doses of niacin should be carefully considered. In patients receiving lovastatin without these concomitant therapies, the incidence of myopathy was approximately 0.1%.

In six patients with cardiac transplants taking immunosuppressive therapy including cyclosporine, concomitantly with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately four times the expected levels. In this group, the therapeutic response also appeared to be proportionately higher, relative to the dosage used.

Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered. Rhabdomyolysis with renal failure has been reported in a renal transplant patient receiving cyclosporine and lovastatin shortly after a dose increase in the systemic antifungal agent itraconazole. Another transplant patient on cyclosporine and a different HMG-CoA reductase inhibitor experienced muscle weakness accompanied by marked elevation of CPK following the initiation of systemic itraconazole therapy. The HMG-CoA reductase inhibitors and the azole derivative antifungal agents inhibit cholesterol biosynthesis at different points in the biosynthetic pathway. In patients receiving cyclosporine, lovastatin should be temporarily discontinued if systemic azole derivative antifungal therapy is

required; patients not taking cyclosporine should be carefully monitored if systemic azole derivative antifungal therapy is required.

Therapy with NU-LOVASTATIN should be discontinued in any patient with an acute, serious condition, suggestive of a myopathy or having a risk factor predisposing to the development of renal failure or rhabdomyolysis, such as severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine or electrolyte disorders and uncontrolled seizures.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

PRECAUTIONS

GENERAL

Before instituting therapy with NU-LOVASTATIN (lovastatin), 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.

USE IN HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (FH)

NU-LOVASTATIN is not effective or is less effective in patients with rare homozygous familial hypercholesterolemia, because these patients have no or very low levels of LDL receptor activity. Lovastatin appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS and SELECTED BIBLIOGRAPHY) in these homozygous patients.

(For Heterozygous Familial Hypercholesterolemia (FH), see PHARMACOLOGY, Clinicial Studies)

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 NU-LOVASTATIN.

EFFECT ON CoQ_{10} LEVELS (UBIQUIONE)

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, NU-LOVASTATIN should be discontinued.

USE IN PREGNANCY

NU-LOVASTATIN is contraindicated during pregnancy (see Teratogenicity and Reproductive Studies under TOXICOLOGY).

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, NU-LOVASTATIN may cause fetal harm when administered to a pregnant woman.

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).

NU-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, NU-LOVASTATIN should be discontinued and the patient apprised of the potential hazard to the fetus.

NURSING MOTHERS

It is not known whether NU-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 NU-LOVASTATIN, women taking NU-LOVASTATIN should not nurse their infants (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 increases 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.

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 NU-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).

Cytochrome P-450 Isoenzyme 3A4 Inhibitors (e.g. cyclosporine, erythromycin, clarithromycin, azithromycin, itraconazole and grapefruit juice)

Concomitant administration of lovastatin with these agents results in a significant increase in plasm concentrations of lovastatin and lovastatin acid. An increased risk of severe myopathy including rhabdomyolysis has been reported in patients who received the concomitant therapy. Concomitant use of lovastatin with the cytochrome P-450 isoform 3A4 inhibitors should be avoided, or the dose of lovastatin should be reduced accordingly (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 (lisinopril).

Coumarin Anticoagulants

Clinically evident bleeding and/or increased prothrombin time have been reported occasionally in patients taking coumarin anticoagulants concomitantly with lovastatin. Careful monitoring of prothrombin time is therefore recommended in such cases.

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 P450 system). Lovastatin had no effect on the pharmacokinetics of antipyrine.

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 of clinically significant adverse interactions.

Drug/Laboratory Test Interactions

Lovastatin may elevate creatine phosphokinase and transaminase levels (see Laboratory Tests under ADVERSE REACTIONS). 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.

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, Pharmacokinetic Interactions and Muscle Effects; PRECAUTIONS, Drug Interactions).

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 possibly, probably or definitely drug-related in any treatment group is shown in the table below.

	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 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.

Effects on the Lens: (see PRECAUTIONS).

POST MARKETING EXPERIENCE

The following additional side effects have been reported since lovastatin was marketed: hepatitis, cholestatic jaundice, vomiting, anorexia, paresthesia, peripheral neuropathy and psychic disturbances including anxiety, erythema multiform, including Stevens-Johnson syndrome; 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 of 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 NU-LOVASTATIN (lovastatin) and should continue on this diet during

treatment with NU-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. Divided doses (i.e., twice daily) tend to be slightly more effective than single daily doses.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of NU-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).

SEVERE HYPERCHOLESTEROLEMIA: In patients with severe hypercholesterolemia, higher dosages (80 mg/day) may be required (see WARNINGS, Muscle Effects and Precautions, Drug Interactions).

PATIENTS WITH ESTABLISHED CORONARY HEART DISEASE

In the trials involving patients with coronary heart disease and administered lovastatin with* (colestipol) or without** 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 PRECAUTION, Drug Interactions, Concomitant Therapy with Other Lipid Metabolism Regulators.

In patients taking immunosuppressive drugs concomitantly with lovastatin, the maximum recommended dosage of NU-LOVASTATIN is 20 mg/day (see WARNINGS, Muscle Effects).

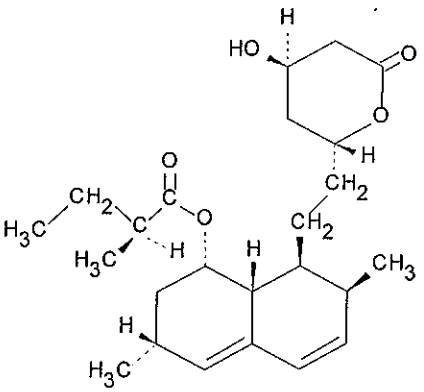
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Lovastatin

Chemical Name: 1) 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(2*S**,-4*S**),8aβ]]-;

Structural Formula:



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

Molecular Weight: 404.55

Description: Lovastatin is a white, odourless, non-hygroscopic crystalline powder.

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* Familial Atherosclerosis Treatment Study (FATS)
**CCAIT, MARS Studies

Solubilities:	Solvent	Solubility (mg/mL)
	Acetonitrile	28
	Ethanol	16
	Methanol	28
	Water	0.44×10^{-3}

The partition coefficient Kp (concentration in organic phase/concentration in aqueous phase) for lovastatin in the octyl alcohol - water system (pH 7 phosphate buffer) is $(1.2 \pm 0.9) \times 10^4$.

COMPOSITION

In addition to lovastatin, each tablet contains the non-medicinal ingredients lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate and FD & C blue #2. NU-LOVASTATIN 20 mg tablets also contain the non-medicinal ingredient FD & C blue #1. NU-LOVASTATIN 40 mg tablets also contain the non-medicinal ingredient D & C yellow #10.

STABILITY AND STORAGE RECOMMENDATIONS

Store at room temperature (15 - 30°C). Protect from light.

AVAILABILITY OF DOSAGE FORMS

NU-LOVASTATIN 20 mg tablets are light blue, octagonal, flat-faced, bevelled-edge tablets, engraved "NU" over "20" on one side. Available in bottles of 100, 250 and 500 tablets.

NU-LOVASTATIN 40 mg tablets are light green, octagonal, flat-faced, bevelled-edge tablets, engraved "NU" over 40 on one side. Available in bottles of 100 and 250 tablets.

INFORMATION TO THE PATIENT

Full prescribing information is available to the physician and pharmacist.

NU-LOVASTATIN is the brand name of Nu·Pharm 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 at room temperature (15°C - 30°C), away from heat and direct light. Keep all medicines 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 (Zocor®), pravastatin (Pravachol®) or fluvastatin (Lescol®) and were allergic, or had reacted badly to it.

- 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

- you have liver disease,

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 (Sandimmune®), gemfibrozil (Lopid®), lipid-lowering doses of niacin (nicotinic acid), nefazodone (Serzone), corticosteroids, an anticoagulant (e.g., warfarin), digoxin erythromycin, clarithromycin, azithromycin or an azole antifungal agent (e.g. itraconazole).

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. Your physician may also arrange for periodic eye examination by an ophthalmologists.

- Do not consume grapefruit juice while taking NU-LOVASTATIN.

- 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 dental or other 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 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.

Active Ingredient: Each tablet of NU-LOVASTATIN contains lovastatin. It comes in two strengths: 20 mg (light blue), and 40 mg (light green).

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

Following an oral dose of ^{14}C-labelled 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-hydroxyacid metabolite are highly bound (>95%) to human plasma proteins. Animal studies demonstrated that lovastatin crosses the blood-brain and placental barriers.

The major active metabolites present in human plasma are the β-hydroxyacid of lovastatin, its 6'-hydroxy, 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 pretreatment 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 and to probucol in a double-blind, parallel study. Both studies were performed with patients with hypercholesterolemia who were at high risk of myocardial infarction. At all dosage levels, lova-

statin produced a significantly greater reduction of total plasma cholesterol, LDL-cholesterol, VLDL-cholesterol, triglycerides, and total cholesterol/HDL-cholesterol ratio when compared to cholestyramine or probucol ($p < 0.01$). The increase in HDL-cholesterol was also significantly greater with lovastatin than with probucol ($p < 0.01$), but not cholestyramine (see Tables III & IV).

Table III
Lovastatin vs. Cholestyramine
(Percent Change from Baseline After 12 Weeks)

Treatment	N	Total-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	Total-C/ HDL-C (mean)	VLDL-C (median)	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

Table IV
Lovastatin vs. Probucol
(Percent Change from Baseline After 14 Weeks)

Treatment	N	Total-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	Total-C/ HDL-C (mean)	VLDL-C (median)	Trig. (median)
Lovastatin								
40 mg q.p.m.	47[a]	-25	-32	+9	-38	-31	-37	-18
80 mg q.p.m.	49	-30	-37	+11	-42	-36	-27	-17
40 mg b.i.d.	47	-33	-40	+12	-45	-39	-40	-25
Probucol 500 mg b.i.d.	97	-10	-8	-23	+26	+23	-13	+1

[a] N=46 for LDL-C, HDL-C, LDL-C/HDL-C, Total-C/HDL-C

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 (≤0.001) (Table V).

Table V
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 2-2½ 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).

[1] Canadian Coronary Atherosclerosis Intervention Trial (CCAIT)

In the second trial[1], 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 ≥ 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.

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 designs to placebo, lovastatin 10-40 mg daily and/or warfarin. Ultrasonograms of the carotid walls were used to determine the

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[3] Familial Atherosclerosis Treatment Study (FATS)

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 hydroxyacid (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.

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 VI.

Table VI
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 am and on at 4:00 pm). Assays were carried out 5-6 hours into light 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%).

Dogs were responsive to the plasma cholesterol-lowering effects of lovastatin and its open hydroxyacid, 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.

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.

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 VII.

Table VII Pharmacokinetic Parameters in Animals

		Intravenous		Oral		
		Dose	AUC	Dose	T_{max}	AUC
Mouse	Lovastatin	0.6	0.38	50	2	8.65
Rat	Lovastatin	0.8	0.776	8	2	1.91
	Open hydroxy acid 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 0-24 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

Lovastatin			
Species	Sex	Route	LD_{50} mg/kg (95% confidence limits)
Rat	Female Male	Oral Oral	>5000 >5000
Mouse	Female Male	Oral Oral	>20 000 >20 000

Open Hydroxy Acid Form of Lovastatin L-154,819			
Species	Sex	Route	LD_{50} mg/kg (95% Confidence Limits)
Mouse	Female	Oral	1230 - 1380
	Male	Oral	1230 - 1380
	Female	Intravenous	272 - 287
	Male	Intravenous	272 - 287
Rat	Female	Oral	≈1260
	Male	Oral	≈1260
	Female	Intraperitoneal	≈113
	Male	Intraperitoneal	≈113

SUBACUTE AND CHRONIC TOXICITY STUDIES

The spectrum of effects produced by lovastatin in mice, rats, rabbits, dogs and monkeys shown in Table VIII below 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	-	N/A	+	-	-
Stomach (non-glandular)	+	+	N/A	N/A	N/A
Fetus	+	+	-	N/T	N/T
Eye (lens)	-	-	-	+	-
Brain (vasculature, optic tract)	-	-	-	+	-
Testes	-	-	-	+	-

+ = Organ affected in some way by drug treatment
- = No effect observed in this organ in this species
N/T = Not tested
N/A = 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 tumours	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 in the table below:

Table X Lovastatin: Key Issues Identified in Safety Assessment - Relationship to Inhibition of HMG-CoA Reductase
Clearly Mechanism-Based - Hepatic morphological 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 tumours in mice · Testicular degeneration in dogs

CARCINOGENICITY AND MUTAGENICITY 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 tumours 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 granular 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.

SELECTED BIBLIOGRAPHY

1) Alberts AW, Chen, J, Kuron G, et al. Mevinolin: a highly potent competitive inhibitor of hydroxymethylglutaryl- coenzyme A reductase and a cholesterol-lowering agent. Proc Natl Acad Sci USA 1980; 77(7): 3957-3961.

2) Bilheimer DW, Grundy SM, Brown MS, Goldstein JL. Mevinolin and colestipol stimulate receptor-mediated clearance of low density lipoprotein from plasma in familial hypercholesterolemia heterozygotes. Proc Natl Acad Sci USA 1983; 80(13): 4124-4128.

3) Bilheimer DW, Grundy SM, Brown MS, Goldstein JL. Mevinolin stimulates receptor-mediated clearance of low density lipoprotein from plasma in familial hypercholesterolemia heterozygotes. Trans Assoc Am Physicians 1983; 96: 1-9.

4) Blankenhorn DH, Azen SP, Kramsch DM, et al. The monitored atherosclerosis regression study (MARS): coronary angiographic changes with lovastatin therapy. Ann Intern Med 1993; 119: 969-976.

5) Bradford RH, Shear CL, Chremos AN, et al. Expanded clinical evaluation of lovastatin (EXCEL) study results. 1. Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. Arch Intern Med 1991; 151: 43-49.

6) Brown BG, Albers JJ, Fisher LD, et al. Regression of coronary artey disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N Eng J Med 1990; 323: 1289-1298.

7) Cashin-Hemphill L, Kramsch DM, Azen P, et al. The monitored atherosclerosis regression study (MARS). On line J of Curr Clin Trials 1992; 1059-2725.

8) De Long DM, et al. A comparison of methods for the estimation of plasma low- and very low-density lipoprotein cholesterol. JAMA 1986; 256: 2372-2377.

9) East C, Alivizatos PA, Grundy SC, et al. Rhabdomyolysis in patients receiving lovastatin after cardiac transplantation. N Engl J Med 1988; 318: 47-48.

10) East CA, Grundy SM, Bilheimer DW. Preliminary report: Treatment of Type 3 hyperlipoproteinemia with mevinolin. Metab Clin Exp 1986; 35(2): 97-98.

11) Effects of lipid-lowering therapy with lovastatin on the progression of coronary atherosclerosis. The Mevinolin (lovastatin) atherosclerosis regression study (MARS). Abstract presented EAS Meeting, Nice France, May 1992.

12) Furberg CD, Adams HP Jr, Applegate WB, et al. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. Circulation 1994; 90(4): 1679-1687.

13) Garg A, Grundy SM. Lovastatin for lowering cholesterol levels in non-insulin-dependent diabetes mellitus. N Engl J Med 1988; 318(2): 81-86.

14) Ghidini A, et al. Congenital abnormalities (VATER) in baby born to mother using lovastatin. Lancet 1992; 339: 1416-1417.

15) Grundy SM. Dietary and drug regulation of cholesterol metabolism in man. Lipid Pharmacol 1976; 2-11: 127.

16) Grundy SM, Bilheimer DW. Inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase by mevinolin in familial hypercholesterolemia heterozygotes: Effects on cholesterol balance. Proc Natl Acad Sci USA 1984; 81(4): 2538-2542.

17) Grundy SM, Vega GL. Effects of mevinolin on plasma lipoprotein (LP) metabolism in moderate hypercholesterolemia. Circulation 1984; 70 (4 Part 3): II 268.

18) Grundy SM, Vega GL. Influence of mevinolin on metabolism of low-density lipoproteins in primary moderate hypercholesterolemia. J Lipid Res 1985: 26(12): 1464-1475.

19) Grundy SM, Vega GL, Bilheimer DW. Influence of combined therapy with mevinolin and interruption of bile-acid reabsorption on low density lipoproteins in heterozygous familial hypercholesterolemia. Ann Intern Med 1985; 103: 339-343.

20) Guirlanda G, Oradei A, Manto A, et al. Evidence of plasma CoQ_{10}-lowering effect by HMG-CoA reductase inhibitors: a double-blind, placebo-controlled study. J Clin Pharmacol 1993; 33: 226-229.

21) Hoeg JM, Maher MB, Bailey KR, Brewer HB. The effects of mevinolin and neomycin alone and in combination on plasma lipid and lipoprotein concentrations in type II hyperlipoproteinemia. Atherosclerosis 1986; 60: 209-214.

22) Hoeg JM, Maher MB, Bailey KR, Brewer HB. Comparison of six pharmacologic regimens for hypercholesterolemia. Am J Cardiol 1987; 59: 812-815.

23) Hoeg JM, Maher MB, Zech LA, et al. Effectiveness of mevinolin on plasma lipoprotein concentrations in type II hyperlipoproteinemia. Am J Cardiol 1986; 57(11): 933-939.

24) Horlick L, LupienP, Beare-Rogers J, et al. Canadian Consensus Conference on Cholesterol, Preliminary Report, Ottawa, Ontario, March 9-11, 1988. CMAJ 1988.

25) Illingworth DR. How effective is drug therapy in heterozygous familial hypercholesterolemia? Am J Cardiol 1993; 72: 54D-58D.

26) Illingworth DR. Comparative efficacy of once versus twice daily mevinolin in the therapy of familial hypercholesterolemia. Clin Pharmacol Ther 1986; 40: 338-343.

27) Illingworth DR. Mevinolin plus colestipol in therapy for severe heterozygous familial hypercholesterolemia. Ann Intern Med 1984; 101(5): 598-604.

28) Illingworth DR, Bacon SP, Larsen KK. Long-term experience with HMG-CoA reductase inhibitors in the therapy of hypercholesterolemia. Atherosclerosis Rev 1988; 18: 161-187.

29) Illingworth DR, Connor WE. Hypercholesterolemia persisting after distal ileal bypass: response to mevinolin. Ann Intern Med 1984; 100(6): 850-851.

30) Illingworth DR, Corbin D. The influence of mevinolin on the adrenal cortical response to corticotropin in heterozygous familial hypercholesterolemia. Proc Natl Acad Sci USA 1985; 82(18): 6291-6294.

31) Illingworth DR, Pappu AS, Bacon SP. Metabolic and clnicial effects of mevinolin in familial hypercholesterolemia. Atherosclerosis 1986; VII: 611-614.

32) Illingworth DR, Sexton GJ. Hypocholesterolemic effects of mevinolin in patients with heterozygous familial hypercholesterolemia. J Clin Invest 1984; 74(6): 1972-1978.

33) Krukemyer JJ, Talbert RL. Lovastatin: a new cholesterol-lowering agent. Pharmacotherapy 1987; 7(6): 198-210.

34) Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial Results. I. Reduction in incidence of coronary heart disease and II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA 1984; 251: 351-374.

35) Mabuchi H, Haba T, Tatami R, et al. Effects of an inhibitor of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase on serum lipoproteins and ubiquinone-10 levels in patients with familial hypercholesterolemia. N Engl J Med 1981; 305 (9): 478-482.

36) Malloy MJ, Kane JP, Kunitake ST, Tun P. Complementarity of colestipol, niacin, and lovastatin in treatment of severe familial hypercholesterolemia. Ann Intern Med 1987; 107(5): 616-623.

37) Norman DJ, et al. Myolysis and acute renal failure in a heart-transplant recipient receiving lovastatin. N Engl J Med 1988; 318(1): 46-47.

38) Quérin S, Lambert R, Cusson JR, et al. Single-dose pharmacokinetics of ^{14}C-lovastatin in chronic renal failure. Clin Pharmacol Ther 1991; 437-441.

39) Scanu AM. Lipoprotein(a) as a cardiovascular risk factor. Trends Cardiovasc Med 1991; 1: 294-299.

40) Smith GD, Song F, Sheldon TA. Cholesterol lowering and mortality: the importance of considering initial level of risk. Br Med J 1993; 306: 1367-1371.

41) Stein EA. Treatment of familial hypercholesterolemia with drugs in children. Atherosclerosis Suppl. 1. 1989; 9: I-145-I-151.

42) Summary of the second report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II). JAMA 1993; 269: 3015-3023.

43) Thompson GR, et al. Efficacy of mevinolin as adjuvant therapy for refractory familial hypercholesterolaemia. Quart J Med 1986; 60(232): 803-811.

44) Tobert JA. Reply to two letters addressed to the Editor in The New England Journal of Medicine. N Engl J Med 1988; 318(1): 48.

45) Tobert JA, Bell GD, Birtwell J, et al. Cholesterol-lowering effect of mevinolin, an inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, in healthy volunteers. J Clin Invest 1982; 69(4): 913-919.

46) Tobert JA, Hitzenberg G, Kukovetz WR, et al. Rapid and substantial lowering of human serum cholesterol by mevinolin (MK-803), an inhibitor of hydroxymethylglutaryl-coenzyme A reductase. Atherosclerosis 1982; 41(1): 61-65.

47) Traber MG, Kayden HJ. Inhibition of cholesterol synthesis by mevinolin stimulates low density lipoprotein receptor activity in human monocyte-derived macrophages. Atherosclerosis 1984; 52(1): 1-11.

48) Uauy R, Vega GL, Grundy SM, Bilheimer DM. Lovastatin therapy in receptor-negative homozygous familial hypercholesterolemia: lack of effect on low-density lipoprotein concentrations or turnover. J Pediatr 1988; 113: 387-392.

49) Vega GL, Grundy SM. Treatment of primary moderate hypercholesterolemia with lovastatin (mevinolin) and colestipol. JAMA 1987; 257(1): 33-38.

50) Waters D, Higginson L, Gladstone P, et al. Effects of monotherapy with an HMG-CoA reductase inhibitor on the progession of coronary atherosclerosis as assessed by serial quantitative arteriography. Circulation 1994; 89(3): 959-968.

51) Waters D, Higginson L, Gladstone P, et al. Design features of a controlled clinical trial to assess the effect of an HMG-CoA reductase inhibitor on the progression of coronary artery disease. Controlled Clin Trials 1993; 14: 45-74.44.

52) Yoshida EM, Levin A. Lovastatin and cholestasis. Can Med Ass J 1993; 148(3): 374.