PRODUCT MONOGRAPH

NU-SIMVASTATIN
(Simvastatin)

5 mg, 10 mg, 20 mg, 40 mg and 80 mg Tablets

Lipid Metabolism Regulator

Nu-Pharm Inc.
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Simvastatin Tablets USP

5 mg, 10 mg, 20 mg, 40 mg and 80 mg

THERAPEUTIC CLASSIFICATION

Lipid Metabolism Regulator

ACTIONS AND CLINICAL PHARMACOLOGY

NU-SIMVASTATIN (simvastatin) is a lipid-lowering agent derived synthetically from lovastatin, a fermentation product.

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-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.

Simvastatin 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.

Simvastatin has complex pharmacokinetic characteristics (see PHARMACOLOGY).

Simvastatin is metabolized by the microsomal hepatic enzyme system (cytochrome P-450 isoform 3A4). The major active metabolites present in human plasma are the β-hydroxyacid of simvastatin and four other active metabolites (see PHARMACOLOGY, Pharmacokinetics).

Comparative Bioavailability

A comparative bioavailability was performed using healthy human volunteers. The rate and extent of absorption of simvastatin was measured following oral administration of 80 mg of either NU-SIMVASTATIN 80 mg tablets or Zocor® 80 mg tablets. The results from measured data are summarized as follows:

Summary Table of the Comparative Bioavailability Data
Simvastatin (Dose: 1 x 80 mg)
From Measured Data – Under Fasting Conditions

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	NU-SIMVASTATIN	Zocor®†	
AUC_T (ng•hr/mL)	64.7 76.6 (59)	74.5 88.6 (59)	87.0
AUC_I (ng•hr/mL)	75.4 101 (101)	82.4 103 (71)	93.6
C_{max} (ng/mL)	11.2 13.4 (62)	13.4 15.5 (53)	84.2
T_{max} (hr)*	1.68 (85)	2.54 (75)	--
$t_{1/2}$ (hr)*	10.94 (82)	9.25 (63)	--

* Arithmetic means (CV%).
** Based on the least squares estimate.
† Zocor® is manufactured by Merck Frosst Canada Inc., and was purchased in Canada.

INDICATIONS AND CLINICAL USE

Coronary Heart Disease

In patients with coronary heart disease and primary hypercholesterolemia, NU-SIMVASTATIN (simvastatin) is indicated to:

- Reduce the risk of total mortality by reducing coronary death;
- Reduce the risk of non-fatal myocardial infarction;
- Reduce the risk for undergoing myocardial revascularization procedures.

In the Scandinavian Simvastatin Survival Study (4S), the effect of therapy with simvastatin on total mortality was assessed in 4444 patients with coronary heart disease (CHD) and baseline total cholesterol (5.5-8.0 mmol/L). In this multicenter, randomized, double-blind, placebo-controlled study, patients with angina or a previous myocardial infarction (MI) were treated with diet and standard care and either simvastatin 20 - 40 mg daily (n=2221) or placebo (n=2223) for a median duration of 5.4 years. Over the course of the study, treatment with simvastatin led to mean reductions in total cholesterol, LDL-cholesterol, and triglycerides of 25%, 35%, and 10%, respectively, and a mean increase in HDL-cholesterol of 8%. Simvastatin reduced the risk of death by 30% (182 deaths in the simvastatin group vs 256 deaths in the placebo group). The risk of CHD death was reduced by 42% (111 vs 189). Simvastatin also decreased the risk of having major coronary events (CHD death plus hospital-verified and silent non-fatal MI) by 34% (431 patients vs 622 patients with one or more events). The risk of having a hospital-verified non-fatal MI was reduced by 37%. Simvastatin reduced the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37% (252 patients vs 383 patients).

Furthermore, posthoc analyses indicate that simvastatin reduced the risk of fatal plus non-fatal cerebrovascular events (stroke and transient ischemic attacks) by 28% (75 patients vs 102 patients). Following the same kind of analyses, in hypercholesterolemic patients with diabetes mellitus, the risk of major coronary events was reduced by 55% (24 patients vs 44 patients).

The 4S study excluded patients with familial hypercholesterolemia (FH) or with congestive heart failure. It is not established to what extent the findings of the 4S study can be extrapolated to these subpopulations of hypercholesterolemic patients (see PHARMACOLOGY, Clinical Studies).

- In patients with heterozygous FH optimal reduction in total and LDL-cholesterol necessitates a combination drug therapy in the majority of patients (see PHARMACOLOGY, Clinical Studies, and BIBLIOGRAPHY).

- Among patients who developed symptoms of heart failure during the 4S study, trends in reduced mortality (19% lower with simvastatin treatment compared to placebo), with reductions of similar magnitude in numbers of patients with major coronary events and numbers of major coronary events were consistent between this group and the total study cohort (see PHARMACOLOGY, Clinical Studies).

Because there were only 57 deaths among the patients with angina alone at baseline and 53 deaths among female patients, the effect of simvastatin on mortality in these subgroups could not be adequately assessed. However, trends in reduced coronary mortality and in major coronary events were consistent between these subgroups and the total study cohort.

(For more details on efficacy results by gender and other pre-defined subgroups, see PHARMACOLOGY, Clinical Studies).

Simvastatin 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 one study in 404 hypercholesterolemic men and women with coronary heart disease*, simvastatin monotherapy was shown to significantly slow the progression of coronary atherosclerosis as assessed by quantitative angiography and significantly reduce the development of both new lesions and new total occlusions (see PHARMACOLOGY, Clinical Studies).

Hyperlipidemia

NU-SIMVASTATIN 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 cholesterol (total-C) and Low-Density Lipoprotein-cholesterol (LDL-C), apolipoprotein B (apo B), and triglycerides (TG) levels in patients with primary hypercholesterolemia (Type IIa)†, or combined (mixed) hyperlipidemia (Type IIb)† when the response to diet and other nonpharmacological measures alone has been inadequate. Simvastatin (5-80 mg/day) reduces the levels of total cholesterol (19-36%), LDL-cholesterol (26-47%), apolipoprotein B (19-38%), and triglycerides (12-24%), in patients with mild to severe hyperlipidemia (Fredrickson Types IIa and IIb). Simvastatin also raises HDL-cholesterol (8-12%) and therefore lowers the LDL-C/HDL-C and total-C/HDL-C ratios.

Limited data is available in homozygous familial hypercholesterolemia (FH). In a controlled clinical study with 12 patients, simvastatin (40 and 80 mg/day) reduced elevated total cholesterol (12% and 23%), LDL-cholesterol (14% and 25%), and apolipoprotein B (14% and 17%),

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* Multicenter Anti-Atheroma Study (MAAS)

† A disorder of lipid metabolism characterized by elevated serum chlolesterol 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.

respectively. One patient with absent LDL-cholesterol receptor function had an LDL-cholesterol reduction of 41% with the 80 mg/day dose (see PHARMACOLOGY, Clinical Studies).

After establishing that the elevation in plasma lipids represents a primary disorder not due to underlying conditions such as poorly-controlled diabetes mellitus, hypothyroidism, the nephrotic syndrome, liver disease, or dysproteinemias, it should ideally be determined that patients for whom treatment with simvastatin 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 HDL-C values, where non-LDL fractions may contribute significantly to total cholesterol levels without apparent increase in cardiovascular risk. In most patients 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 less accurate. In such patients, LDL-cholesterol may be obtained by ultra centrifugation.

[††] DeLong DM, et al. A comparison of methods. JAMA 1986;256:2372-77.

CONTRAINDICATIONS

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

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 certain metabolic pathways in the cytochrome P-450 system. Simvastatin is metabolized by the cytochrome P-450 isoform 3A4 and as such may interact with agents which inhibit this enzyme (see Myopathy/Rhabdomyolysis and PRECAUTIONS, Drug Interactions and Cytochrome P-450 Inhibitors).

Myopathy/Rhabdomyolysis

Simvastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as muscle pain or weakness associated with grossly elevated creatine phosphokinase (CPK) (> 10x the upper limit of normal [ULN]). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

In the Scandinavian Simvastatin Survival Study, there was one case of myopathy among 1399 patients taking simvastatin 20 mg and no cases among 822 patients taking 40 mg daily for a median duration of 5.4 years. In two 6-month controlled clinical studies, there was one case of myopathy among 436 patients taking 40 mg and 5 cases among 669 patients taking 80 mg. The risk of myopathy is increased by concomitant therapy with certain drugs, some of which were excluded by the designs of these studies.

Myopathy/Rhabdomyolysis Caused by Drug Interactions

The risk of myopathy/rhabdomyolysis is increased by concomitant use of simvastatin with the following:

- **Potent inhibitors of CYP3A4: Cyclosporine, the antifungal azoles itraconazole, and ketoconazole, the macrolide antibiotics erythromycin and clarithromycin, HIV protease inhibitors, or the antidepressant nefazodone, particularly with higher doses of simvastatin** (see PRECAUTIONS, Drug Interactions, PHARMACOLOGY, Pharmacokinetics).

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

- **Other Drugs: Amiodarone or verapamil with higher doses of simvastatin** (see PRECAUTIONS, Drug Interactions).

The risk of myopathy/rhabdomyolysis is dose related. The incidence in clinical trials, in which patients were carefully monitored and some interacting drugs were excluded, has been approximately 0.03% at 20 mg, 0.08% at 40 mg and 0.4% at 80 mg.

Reducing the Risk of Myopathy/Rhabdomyolysis

1. General measures

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

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

2. **Measures to reduce the risk of myopathy/rhabdomyolysis caused by drug interactions (see above)**

Use of simvastatin concomitantly with itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, or nefazodone should be avoided. If treatment with itraconazole, ketoconazole, erythromycin, or clarithromycin is unavoidable, therapy with simvastatin should be suspended during the course of treatment. Concomitant use with other medicines labeled as having a potent inhibitory effect on CYP3A4 at therapeutic doses should be avoided unless the benefits of combined therapy outweigh the increased risk.

The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with cyclosporine, gemfibrozil, other fibrates or lipid-lowering doses (1 g/day) of niacin. The combined use of simvastatin with fibrates or niacin should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination. Addition of these drugs to simvastatin typically provides little additional reduction in LDL-C, but further reductions of TG and further increases in HDL-C may be obtained. Combinations of fibrates or niacin with low doses of simvastatin have been used without myopathy in small, short-term clinical studies with careful monitoring.

The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone or verapamil. The combined use of simvastatin at doses higher than 20 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy.

Hepatic Effects

In clinical studies, marked persistent increases (to more than 3 times the ULN) in serum transaminases have occurred in 1% of adult patients who received simvastatin (see ADVERSE REACTIONS, Laboratory Tests). When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. Some of these patients had abnormal liver function tests prior to therapy with simvastatin and/or consumed substantial quantities of alcohol.

In the Scandinavian Simvastatin Survival Study (see PHARMACOLOGY, Clinical Studies), the number of patients with more than one transaminase elevation to > 3 times the ULN, over the course of the study, was not significantly different between the simvastatin and placebo groups (14 [0.7%) vs. 12 [0.6%]). The frequency of single elevations of SGPT (ALT) to 3 times the ULN was significantly higher in the simvastatin group in the first year of the study (20 vs. 8, p=0.023), but not thereafter. Elevated transaminases resulted in the discontinuation of 8 patients from therapy in the simvastatin group (n=2221) and 5 in the placebo group (n=2223). Of the 1986 simvastatin treated patients in 4S with normal liver function tests (LFTs) at baseline, only 8 (0.4%) developed consecutive LFT elevations to >3 times the ULN and/or were discontinued due to transaminase elevations during the 5.4 years (median follow-up) of the study. All of the patients in this study received a starting dose of 20 mg of simvastatin; 37% were titrated to 40 mg.

In 2 controlled clinical studies in 1105 patients, the 6 month incidence of persistent hepatic transaminase elevations considered drug-related was 0.7% and 1.8% at the 40 and 80 mg dose, respectively.

It is recommended that liver function tests be performed at baseline and periodically thereafter (e.g., semiannually) for the first year of treatment or until one year after the last elevation in dose in all patients. Patients titrated to the 80 mg dose should receive an additional test at 3 months. Special 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 ULN 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 persistent transaminase elevations are contraindications to the use of NU-SIMVASTATIN; if such a condition should develop during therapy, the drug should be discontinued.

Moderate (less than three times the ULN) elevations of serum transaminases have been reported following therapy with simvastatin (see ADVERSE REACTIONS). These changes were not specific to simvastatin and were also observed with comparative lipid-lowering agents. They generally appeared within the first 3 months after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptom and did not require interruption of treatment.

PRECAUTIONS

General

Before instituting therapy with NU-SIMVASTATIN (simvastatin), an attempt should be made to control hypercholesterolemia with appropriate diet and 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 simvastatin or any other lipid-lowering agent.

In primary prevention intervention the effects of simvastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity or mortality or total mortality have not been established.

Patients with Severe Hypercholesterolemia

Higher dosages (40-80 mg/day) required for some patients with severe hypercholesterolemia are associated with increased plasma levels of simvastatin. **Caution should be exercised in such patients who are also significantly renally impaired, elderly or are concomitantly administered P-450 inhibitors (see WARNINGS, Myopathy/Rhabdomyolysis and PRECAUTIONS, Drug Interactions).**

Effect on the Lens

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

Effect on CoQ_{10} Levels (Ubiquinone)

Significant decreases in circulating CoQ_{10} levels in patients treated with simvastatin and other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of CoQ_{10} has not been established (see BIBLIOGRAPHY).

Effect on Lipoprotein(a)

In some patients, the beneficial effect of lowered total cholesterol and LDL-C levels may be partly blunted by a concomitant increase in the Lipoprotein(a) [Lp(a)] level. Further research is currently ongoing to elucidate the significance of Lp(a) plasma level variations. Therefore, until further experience is obtained, it is suggested, when feasible, that Lp(a) measurements be carried out in patients placed on therapy with NU-SIMVASTATIN.

Hypersensitivity

In few instances eosinophilia and skin eruptions appear to be associated with simvastatin treatment. If hypersensitivity is suspected, NU-SIMVASTATIN should be discontinued.

Use in Pregnant Women

NU-SIMVASTATIN is contraindicated during pregnancy (see TOXICOLOGY, Teratogenicity and Reproductive Studies).

Safety in pregnant women has not been established. No controlled clinical trials with simvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. However, in an analysis of approximately 200 prospectively followed pregnancies exposed during the first trimester to simvastatin or another closely related HMG-CoA reductase inhibitor, the incidence of congenital anomalies was comparable to that seen in the general population. This number of pregnancies was statistically sufficient to exclude a 2.5-fold or greater increase in congenital anomalies over the background incidence.

Although there is no evidence that the incidence of congenital anomalies in offspring of patients taking simvastatin or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with simvastatin may reduce the fetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering drugs during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolemia. For these reasons, NU-SIMVASTATIN should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with NU-SIMVASTATIN should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant. (See CONTRAINDICATIONS and BIBLIOGRAPHY).

Nursing Mothers

It is not known whether simvastatin or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions, women taking NU-SIMVASTATIN should not nurse (see CONTRAINDICATIONS).

Pediatric Use

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

Elderly

For patients over the age of 65 years who received simvastatin in controlled clinical studies, efficacy, as assessed by reduction in total and LDL-cholesterol levels, appeared similar to that

seen in the population as a whole, and there was no apparent increase in the frequency and severity of clinical or laboratory adverse findings.

Use in Patients with Impaired Renal Function

Simvastatin 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 <30 mL/min), dosages above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously. This recommendation is based on studies with lovastatin (see WARNINGS, Myopathy/Rhabdomyolysis).

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 simvastatin and other HMG-CoA reductase inhibitors have suggested that these agents do not reduce plasma cortisol concentration or impair adrenal reserve and do not reduce basal plasma testosterone concentration. However, the effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary -gonadal axis in premenopausal women are unknown.

Patients treated with simvastatin 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 simvastatin and the bile acid sequestrant, cholestyramine, are additive.

When simvastatin 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 simvastatin may be impaired by the resin.

Gemfibrozil and other Fibrates, Lipid-lowering Doses (≥1g/day) of Niacin (Nicotinic Acid): These drugs increase the risk of myopathy when given concomitantly with simvastatin, probably because they can produce myopathy when given alone (see WARNINGS, Myopathy/Rhabdomyolysis Caused by Drug Interactions). There is no evidence to suggest that these agents affect the pharmacokinetics of simvastatin.

Myopathy, including rhabdomyolysis, has occurred in patients who were receiving co-administration of simvastatin and other HMG-CoA reductase inhibitors with fibric acid derivatives and niacin, particularly in subjects with pre-existing renal insufficiency (see WARNINGS, Myopathy/Rhabdomyolysis caused by drug interactions).

Erythromycin and Clarithromycin: see WARNINGS, Measures to reduce the risk of myopathy/rhabdomyolysis caused by drug interactions.

Coumarin Anticoagulants: In two clinical studies, one in normal volunteers and the other in hypercholesterolemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratios (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Digoxin: Concomitant administration of simvastatin and digoxin in normal volunteers resulted in a slight elevation (<0.3 ng/mL) in drug concentrations (as measured by a digoxin radioimmunoassay) in plasma compared to concomitant administration of placebo and digoxin.

Cytochrome P-450 Inhibitors: Simvastatin has no CYP3A4 inhibitory activity; therefore, it is not expected to affect plasma levels of other drugs metabolized by CYP3A4 (see PHARMACOLOGY, Pharmacokinetics). However, simvastatin itself is a substrate for CYP3A4. Potent inhibitors of CYP3A4 increase the risk of myopathy by increasing the plasma levels of HMG-CoA reductase inhibitory activity during simvastatin therapy. These include cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, and nefazodone (see WARNINGS, Myopathy/Rhabdomyolysis Caused by Drug Interactions).

Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma levels of drugs metabolized by CYP3A4. The effect of typical consumption (one 250-ml

glass daily) is minimal (13% increase in active plasma HMG-CoA reductase inhibitory activity as measured by the area under the concentration-time curve) and of no clinical relevance. However, very large quantities (over 1 liter daily) significantly increase the plasma levels of HMG-CoA reductase inhibitory activity during simvastatin therapy and should be avoided (see WARNINGS, Myopathy/Rhabdomyolysis Caused by Drug Interactions).

Amiodarone: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone with higher doses of simvastatin (see WARNINGS, Myopathy/Rhabdomyolysis Caused by Drug Interactions). In an ongoing clinical trial, myopathy has been reported in 6% of patients receiving simvastatin 80 mg and amiodarone.

Verapamil: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of verapamil with higher doses of simvastatin (see WARNINGS, Myopathy/Rhabdomyolysis Caused by Drug Interactions). In an analysis of clinical trials involving 33,796 patients treated with simvastatin 20 to 80 mg, the incidence of myopathy was higher in patients receiving verapamil and simvastatin (0.54%) than in patients taking simvastatin without a calcium channel blocker (0.10%).

Other Concomitant Therapy: In clinical studies, simvastatin was used concomitantly with angiotensin converting enzyme (ACE) inhibitors, beta-blockers, diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence, to date, of clinically significant adverse interactions.

Drug/Laboratory Test Interactions: Simvastatin may elevate serum transaminase and creatine phosphokinase levels (from skeletal muscles) (see ADVERSE REACTIONS, Laboratory Tests).

In the differential diagnosis of chest pain in a patient on therapy with simvastatin, cardiac and noncardiac fractions of these enzymes should be determined.

ADVERSE REACTIONS

Based on experience in a total of over 2300 patients, of whom more than 1200 were treated for one year and over 230 for 2 years or more, simvastatin is generally well tolerated and adverse reactions are usually mild and transient.

In pre-marketing controlled clinical studies, 1.0% of patients were withdrawn due to adverse experiences attributable to simvastatin.

Adverse experiences occurring at an incidence of ≥ 0.5% of 2361 patients treated with simvastatin in pre-marketing controlled clinical studies and reported to be possibly, probably or definitely drug related are shown in the table below:

	SIMVASTATIN (n=2361) %
Gastrointestinal	
Abdominal Pain	2.2
Acid Regurgitation	0.5
Constipation	2.5
Dyspepsia	0.6
Diarrhea	0.8
Flatulence	2.0
Nausea	1.1
Nervous System	
Headache	1.0
Skin	
Rash	0.7
Miscellaneous	
Asthenia	0.8

In the Scandinavian Simvastatin Survival Study (4S) (see PHARMACOLOGY, Clinical Studies) involving 4444 patients treated with 20-40 mg/day of simvastatin (n=2221) or placebo (n=2223), the safety and tolerability profiles were comparable between groups over the median 5.4 years of the study.

Ophthalmological Observations: see PRECAUTIONS, Effect on the Lens.

Laboratory Tests

Marked persistent increases of serum transaminases (ALT, AST) have been noted (see WARNINGS).

About 5.0% of patients had elevations of creatine phosphokinase (CPK) levels three or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CPK. Myopathy has been reported rarely (see WARNINGS, Myopathy/Rhabdomyolysis and PRECAUTIONS, Drug/Laboratory Test Interactions).

The following additional adverse reactions were reported either in uncontrolled clinical studies or in marketed use; however a causal relationship to therapy with simvastatin has not been established.

Dermatologic

Erythema Multiforme including Stevens-Johnson Syndrome

Gastrointestinal

Vomiting

Hematologic

Anemia

Leukopenia

Purpura

Hepatic

Rarely hepatitis

Jaundice

Musculoskeletal

Rarely rhabdomyolysis

Muscle cramps

Myalgia

Nervous System/Psychiatric

Dizziness

Paresthesia

Depression

Peripheral Neuropathy: Rarely, peripheral neuropathy with muscle weakness or sensory disturbance has been reported (see BIBLIOGRAPHY).

Skin

Rash

Pruritus

Alopecia

Miscellaneous

Pancreatitis

Laboratory Tests

Elevated alkaline phosphatase and γ-glutamyl transpeptidase have been reported.

An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features:

- Angioedema
- Arthralgia
- Arthritis
- Dermatomyositis
- Dyspnea
- Eosinophilia
- ESR increased
- Fever
- Flushing
- Lupus-like Syndrome
- Malaise
- Photosensitivity
- Polymyalgia rheumatica
- Thrombocytopenia
- Urticaria
- Vasculitis

Others

Although the following adverse reactions were not observed in clinical studies with simvastatin, they have been reported following treatment with other HMG-CoA reductase inhibitors: anorexia, psychic disturbances including anxiety, and hypospermia.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

A few cases of overdosage have been reported; no patient had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 450 mg.

In the event of overdosage, treatment should be symptomatic and supportive, liver function should be monitored, and appropriate therapy instituted.

The dialyzability of simvastatin and its metabolites is not known.

DOSAGE AND ADMINISTRATION

The patient should be placed on a diet, at least an equivalent of the American Heart Association (AHA) step 1, before receiving NU-SIMVASTATIN (simvastatin) and should continue on this diet

during treatment with the drug. If appropriate, a program of weight control and physical exercise should be implemented.

The recommended dose range for most patients is 10 to 40 mg/day. The maximum dose is 80 mg/day, which may be required in a minority of patients unable to achieve the Canadian cholesterol guidelines or NCEP reductions with lower doses.

Coronary Heart Disease

Patients with coronary heart disease and primary hypercholesterolemia can be treated with a starting dose of 20 mg/day given as a single dose in the evening. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80 mg daily given as a single dose in the evening.

Hyperlipidemia

The usual starting dose is 10 mg/day given as a single dose in the evening. Patients with mild to moderate hypercholesterolemia can be treated with a starting dose of 5 mg of NU-SIMVASTATIN. Adjustments of dosage, if required, should be made as specified above (see DOSAGE AND ADMINISTRATION, Coronary Heart Disease).

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

Concomitant Therapy

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

In patients taking cyclosporine, gemfibrozil, other fibrates or lipid lowering doses (≥1g/day) of niacin concomitantly with NU-SIMVASTATIN, the dose of NU-SIMVASTATIN should not exceed 10 mg/day. In patients taking amiodarone or verapamil concomitantly with NU-SIMVASTATIN, the dose of NU-SIMVASTATIN should not exceed 20 mg/day (see WARNINGS, Measures to reduce the risk of myopathy/rhabdomyolysis caused by drug interactions and PRECAUTIONS, Drug Interactions).

PHARMACEUTICAL INFORMATION

Drug Substance

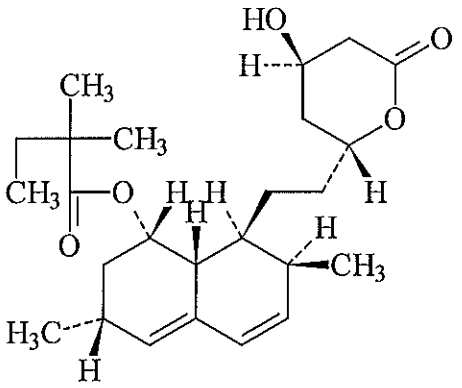
Proper Name: Simvastatin

Chemical Name: [1 S-[1α,3α,7ß 8ß(2S*,4S*), 8aß]]-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl 2,2-dimethylbutanoate.

Empirical Formula: $C_{25}H_{38}O_5$

Molecular Weight: 418.58

Structural Formula:



Description: Simvastatin is a white crystalline powder.

Solubilities:

Solvent	Solubility (mg/mL)
Chloroform	610
Methanol	200
Ethanol	160
Water	0.03

The partition coefficient, Kp (where Kp = concentration in organic phase/concentration in aqueous phase) determined for simvastatin in either the 1-octanol-pH 4 acetate buffer system or the 1-octanol-pH 7.2 acetate buffer system is > 1995.

Composition

In addition to simvastatin, each tablet contains the non-medicinal ingredients butylated hydroxyanisole, croscarmellose sodium, hydroxyethyl cellulose, lactose monohydrate,

magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80 and titanium dioxide. NU-SIMVASTATIN 5 and 20 mg tablets also contain yellow ferric oxide. NU-SIMVASTATIN 10, 20, 40 and 80 mg tablets also contain red ferric oxide.

Stability and Storage Recommendations

Store at room temperature (15 to 30°C).

AVAILABILITY OF DOSAGE FORMS

NU-SIMVASTATIN 5 mg Tablets: each light yellow, shield-shaped, biconvex, straight-edged, film-coated tablet, engraved NU on one side and 5 on the other, contains 5 mg simvastatin. Available in bottles of 100 and 500.

NU-SIMVASTATIN 10 mg Tablets: each light pink, shield-shaped, biconvex, straight-edged, film-coated tablet, engraved NU on one side and 10 on the other, contains 10 mg simvastatin. Available in bottles of 100 and 500.

NU-SIMVASTATIN 20 mg Tablets: each peach, shield-shaped, biconvex, straight-edged, film-coated tablet, engraved NU on one side and 20 on the other, contains 20 mg simvastatin. Available in bottles of 100, 250 and 500.

NU-SIMVASTATIN 40 mg Tablets: each dusty rose, shield-shaped, biconvex, straight-edged, film-coated tablet, engraved NU on one side and 40 on the other, contains 40 mg simvastatin. Available in bottles of 100 and 500.

NU-SIMVASTATIN 80 mg Tablets: each dusty rose, capsule-shaped, biconvex, straight-edged, film-coated tablet, engraved NU on one side and 80 on the other, contains 80 mg simvastatin. Available in bottles of 100.

INFORMATION FOR THE PATIENT

The Product Monograph is available upon request to physicians and pharmacists.

NU-SIMVASTATIN is the brand name of Nu-Pharm Inc. for the substance -simvastatin, available only on prescription from your physician. Simvastatin is one of a class of medicines known as HMG-CoA reductase inhibitors. 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. Simvastatin is used to lower the levels of cholesterol (particularly Low Density Lipoprotein (LDL) cholesterol) and fatty substances called triglycerides in your blood.

Your physician has prescribed NU-SIMVASTATIN to reduce the amount of cholesterol and triglycerides in your blood. Elevated cholesterol can cause coronary heart disease (CHD) by clogging the blood vessels which carry oxygen and nutrients to the heart. If you have CHD and elevated cholesterol levels, your physician has prescribed NU-SIMVASTATIN to help reduce the risk of dying from coronary heart disease, to lessen the risk of a heart attack or stroke, and to decrease the risk of needing a surgical procedure to increase the blood flow to your heart.

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 in a tightly closed container 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 simvastatin or any other medication in the same class - example, atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor) or pravastatin (Pravachol) - and were allergic, or reacted badly to it.
- You have liver disease.
- You are pregnant or intend to become pregnant. This medicine should not be used in women who are pregnant, trying to become pregnant or suspect that they are pregnant. If you become pregnant while taking NU-SIMVASTATIN, stop taking it and contact your physician immediately.
- You are breast-feeding or intend to breast-feed.

TAKING NU-SIMVASTATIN WITH OTHER MEDICINES

You should tell your physician about all drugs that you are using or plan to use, including those obtained without a prescription, while taking NU-SIMVASTATIN. You should also tell any physician who is prescribing a new medication for you that you are taking NU-SIMVASTATIN.

Because taking NU-SIMVASTATIN with any of the following drugs can increase the risk of muscle problems (see Side effects of this medicine - and what you should do), it is particularly important to tell your physician if you are taking:

- cyclosporine (immunosuppressant)
- antifungal agents (itraconazole or ketaconazole)
- fibric acid derivatives (bezafibrate, fenofibrate, and gemfibrozil) (drug to treat lipids problems)
- the antibiotics (erythromycin and clarithromycin)
- HIV protease inhibitors (indinavir, nelfinavir, ritonavir and saquinavir)
- the antidepressant nefazodone
- amiodarone (a drug used to treat an irregular heartbeat)
- verapamil (a drug used to treat high blood pressure or angina)
- large doses (more than 1 g/day) of niacin (nicotinic acid) (drug to treat lipids problems)

It is also important to tell your doctor if you are taking corticosteroids, anticoagulants (drug that prevents blood clots, such as warfarin) or digoxin (a drug used to treat heart problems).

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.

- When taking NU-SIMVASTATIN, you should avoid consuming very large amounts (over 1 liter daily) of grapefruit juice; however, typical consumption (one 250-mL glass daily) is unlikely to cause any problems.

- 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 or pharmacist.

- 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 physician in charge that you are taking this medicine.

- Store your tablets at room temperature (15 to 30°C), in a tightly closed container, away from heat and direct light, and out of damp places, such as the bathroom or kitchen.

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

Since muscle problems are on rare occasions serious, you should contact your physician promptly if you experience muscle pain, tenderness, or weakness.

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

- 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 NU-SIMVASTATIN contains simvastatin. It comes in five strengths: 5 mg (light yellow), 10 mg (light pink), 20 mg (peach), 40 mg (dusty rose) and 80 mg (dusty rose).

Non-medicinal ingredients (alphabetical): butylated hydroxyanisole, croscarmellose sodium, hydroxyethyl cellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80 and titanium dioxide. NU-SIMVASTATIN 5 mg and 20 mg tablets also contain yellow ferric oxide. NU-SIMVASTATIN 10 mg, 20 mg, 40 mg and 80 mg tablets also contain red ferric oxide.

PHARMACOLOGY

Human Pharmacology

Simvastatin has been shown to reduce both normal and elevated LDL-cholesterol concentrations. The involvement of LDL-cholesterol in atherogenesis has been well-documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological studies have established that high total-C, LDL-cholesterol, and apo B are risk factors for coronary heart

disease, while high HDL-C and apo A-I are associated with decreased risk. In primary prevention intervention the effect of simvastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity or mortality or total mortality have 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 simvastatin 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 simvastatin. Since each LDL particle contains one molecule of apolipoprotein B, and since little apolipoprotein B is found in other lipoproteins, this strongly suggests that simvastatin 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) during treatment with simvastatin cannot be excluded. In addition, simvastatin increases total HDL-cholesterol and reduces VLDL-cholesterol and plasma triglycerides (see Tables I - V under Clinical Studies).

The active ß-hydroxyacid form of simvastatin 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 simvastatin would not be expected to cause an accumulation of potentially toxic sterols. In addition, HMG-CoA is metabolized readily back to acetyl-CoA, which participates in many biosynthetic processes in the body.

Although cholesterol is the precursor of all steroid hormones, studies with simvastatin have suggested that this agent has no clinical effect on steroidogenesis (see PRECAUTIONS, Endocrine Function). Simvastatin caused no increase in biliary lithogenicity and, therefore, would not be expected to increase the incidence of gallstones.

Pharmacokinetics

Simvastatin is a hydrophobic lactone which is readily hydrolyzed *in vivo* to the corresponding ß - hydroxyacid, a potent inhibitor of HMG-CoA reductase. Simvastatin undergoes extensive first pass extraction in the liver, the target organ for the inhibition of HMG-CoA reductase and the primary site of action. This tissue selectivity (and consequent low systemic exposure) of orally administered simvastatin has been shown to be far greater than that observed when the drug is administered as the enzymatically active form, i.e. as the open hydroxyacid. 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). Both are measured in plasma following administration of simvastatin.

Following an oral dose of ^{14}C-labelled simvastatin in man, 13% of the dose is excreted in urine and 60% in feces. The latter represents absorbed drug equivalents excreted in bile, as well as unabsorbed drug.

In a single dose study in nine healthy subjects, it was estimated that less than 5% of an oral dose of simvastatin reached the general circulation in the form of active inhibitors. Following administration of simvastatin tablets, the coefficient of variation, based on between-subject variability, was approximately 48% for the area under the curve (AUC) of total inhibitory activity in the general circulation.

Both simvastatin and its β-hydroxyacid metabolite are bound (>94%) to human plasma proteins. Animal studies have not been performed to determine whether simvastatin crosses the placental barrier.

Simvastatin is metabolized by the microsomal hepatic enzyme system (cytochrome P-450 isoform 3A4). The major active metabolites present in human plasma are the β-hydroxyacid of simvastatin and four other active metabolites. Peak plasma concentrations of both active and total inhibitors were attained within 1.3 to 2.4 hours post-dose. While the recommended therapeutic dose range is 10 to 40 mg/day, there was no substantial deviation from linearity of AUC of inhibitors in the general circulation with an increase in dose to as high as 120 mg. Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before a test meal.

In a study of patients with severe renal insufficiency (creatinine clearance < 30 mL/min), the plasma concentrations of total inhibitors after a single dose of a related HMG-CoA reductase inhibitor were approximately two-fold higher than those in healthy volunteers.

In a study of 12 healthy volunteers, simvastatin at the maximal 80-mg dose had no effect on the metabolism of the probe CYP3A4 substrates midazolam and erythromycin. This indicates that simvastatin is not an inhibitor of CYP3A4, and therefore, is not expected to affect the plasma levels of other drugs metabolized by CYP3A4.

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

Clinical Studies

Simvastatin has been shown to be highly effective in reducing total and LDL-cholesterol in 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 long-term therapy. When therapy with simvastatin is stopped, total cholesterol has been shown to return to pretreatment levels.

In a multicenter, double-blind, placebo-controlled, dose-response study in patients with primary hypercholesterolemia (Table I), simvastatin given as a single dose in the evening was similarly effective as when given on a twice daily basis. Simvastatin consistently decreased total plasma cholesterol (TOTAL-C), LDL-cholesterol (LDL-C), total cholesterol/ HDL-cholesterol (TOTAL-C/HDL-C) ratio, LDL-cholesterol /HDL-cholesterol (LDL-C/HDL-C) ratio and triglycerides (TRIG), and slightly increased HDL-cholesterol (HDL-C).

TABLE I

Dose Response in Patients with Primary Hypercholesterolemia

(Percent Change from Baseline After 4 Weeks)

TREATMENT	**N**	**TOTAL-C** (mean)	**LDL-C** (mean)	**HDL-C** (mean)	**LDL-C/ HDL-C** (mean)	**TOTAL-C/ HDL-C** (mean)	**TRIG.** (mean)
SIMVASTATIN							
10 mg q.p.m.	38	-21	-24	+11	-31	-29	-21
40 mg q.p.m.	39	-33	-39	+8	-44	-39	-27

The results of 3 separate studies depicting the dose response to simvastatin in patients with primary hypercholesterolemia are presented in TABLE II:

TABLE II

Dose Response in Patients with Primary Hypercholesterolemia

(Mean Percent Change from Baseline After 6 to 24 Weeks)

TREATMENT		N	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	TRIG (median)
Lower Dose Comparative Study						
Simvastatin	-5 mg*	109	-19	-26	10	-12
	-10 mg*	110	-23	-30	12	-15
Scandinavian Simvastatin Survival Study						
Placebo		2223	-1	-1	0	-2
Simvastatin	-20* mg	2221	-28	-38	8	-19
Upper Dose Comparative Study						
Simvastatin	-40* mg	433	-31	-41	9	-18
	-80* mg	664	-36	-47	8	-24

* In the evening

One third of patients obtained a reduction in LDL-cholesterol of 53% or more at the 80 mg dose. The percent reduction in LDL-cholesterol was essentially independent of the baseline level. In contrast, the percent reduction in triglycerides was related to the baseline level of triglycerides. Of the 664 patients randomized to 80 mg, 475 patients with plasma triglycerides ≤2.25 mmol/L (200 mg/dL) had a median reduction in triglycerides of 21%, while in 189 patients with hypertriglyceridemia > 2.25 mmol/L (200 mg/dL), the median reduction in triglycerides was 36%. In these studies, patients with triglycerides > 4.0 mmol/L (350 mg/dL) were excluded.

In a controlled clinical study, 12 patients 15-39 years of age with homozygous familial hypercholesterolemia received simvastatin 40 mg/day in a single dose or in 3 divided doses, or 80 mg/day in 3 divided doses. The mean LDL-cholesterol reductions for the 40 mg and 80 mg doses were 14% and 25%, respectively. One patient with absent LDL-cholesterol receptor function had an LDL-cholesterol reduction of 41% with the 80 mg dose.

In a separate randomized 12-week multicenter study, simvastatin at dosages of 20 and 40 mg was compared in patients with familial (n=112) and non-familial (n=54) hypercholesterolemia. After 12 weeks on the two simvastatin doses, reductions in total and LDL-cholesterol were as shown in Table III.

TABLE III

Simvastatin in FH and NON-FH Patients

(Percent Change from baseline after 12 weeks)

	TOTAL CHOLESTEROL CHANGE,%		LDL CHOLESTEROL CHANGE, %	
	Simvastatin 20 mg	Simvastatin 40 mg	Simvastatin 20 mg	Simvastatin 40 mg
Baseline Total Cholesterol				
<7.76 mmol/L	-25	-32	-32	-42
≥7.76 mmol/L	-27	-33	-32	-40
Primary Diagnosis:				
Heterozygous FH	-26	-34	-30	-41
Non-familial hypercholesterolemia	-28	-30	-37	-40

While these results show that the lipid effects of simvastatin in heterozygous FH may be comparable in magnitude to those observed in patients with non-familial hypercholesterolemia, long-term optimal reduction in total and LDL-cholesterol necessitates combination drug therapy in the majority of patients suffering from heterozygous FH (see BIBLIOGRAPHY).

Simvastatin was compared to cholestyramine, or gemfibrozil respectively, in double-blind parallel studies. All studies were performed in patients who exhibited moderate to high hypercholesterolemia and thus were thought to be at higher than average risk of coronary events. Results of these studies are summarized in Tables IV, V, VI.

TABLE IV

Simvastatin 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 (mean)	TRIG. (mean)
Simvastatin								
20 mg q.p.m.	84	-27	-32	+10	-36	-31	-8	-13
40 mg q.p.m.	81	-33	-41	+10	-45	-38	-28	-21
Cholestyramine								
4-24 g/day†	85	-15	-21	+8	-25	-19	+7	+15

† Maximum tolerated dose.

TABLE V

Simvastatin 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)	TRIG. (mean)
Simvastatin							
20 and 40 mg q.p.m.	177	-33	-41	+15	-46	-39	-10
Cholestyramine							
4 to 12 g b.i.d.	84	-21	-30	+10	-35	-26	+36

TABLE VI

Simvastatin vs. Gemfibrozil

(Percent change from Baseline After 12 Weeks)

TREATMENT	N	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	VLDL-C (mean)	TRIG. (mean)
Simvastatin 5 to 10 mg (Stratum I)†	68	-21	-26	+7	-28	-25	-10
Simvastatin 10 to 20 mg (Stratum II) ††	78	-27	-34	+9	-37	-18	-7
Gemfibrozil (Stratum I)	69	-15	-18	+17	-25	-37	-31
Gemfibrozil (Stratum II)	75	-15	-17	+16	-22	-49	-32

† (Stratum I, baseline LDL <195 mg/dL)
†† (Stratum II, baseline LDL ≥ 195 mg/dL)

At all dosage levels tested, simvastatin produced a significantly greater reduction of total plasma cholesterol, LDL-cholesterol, VLDL-cholesterol, triglycerides, and total cholesterol/HDL-cholesterol ratio than did cholestyramine. Simvastatin produced an increase in HDL-cholesterol greater than did cholestyramine; this increase, however, was inferior to that observed with the fibrates such as gemfibrozil. Simvastatin produced a significantly greater reduction of total plasma cholesterol and LDL-cholesterol when compared to gemfibrozil.

In the Scandinavian Simvastatin Survival Study (4S), the effect of therapy with simvastatin on total mortality was assessed in 4444 patients with coronary heart disease (CHD) and baseline total cholesterol 212-309 mg/dL (5.5-8.0 mmol/L). In this multicenter, randomized, double-blind, placebo-controlled study, patients with angina or a previous myocardial infarction (MI) were treated with diet and standard care and either simvastatin 20-40 mg daily (n=2221) or placebo (n=2223) for a median duration of 5.4 years. Over the course of the study, treatment with

simvastatin led to mean reductions in total cholesterol, LDL-cholesterol, and triglycerides of 25%, 35%, and 10%, respectively, and a mean increase in HDL-cholesterol of 8%. Simvastatin reduced the risk of death (Figure 1) by 30%, p=0.0003 (182 deaths in the simvastatin group vs 256 deaths in the placebo group). The risk of CHD death was reduced by 42% (111 vs 189). Simvastatin also decreased the risk of having major coronary events (CHD death plus hospital-verified and silent non-fatal MI) (Figure 2) by 34%, p<0.00001 (431 patients vs 622 patients with one or more events). The risk of having a hospital-verified non-fatal MI was reduced by 37%. Simvastatin reduced the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37%, p<0.00001 (252 patients vs 383 patients). Furthermore, posthoc analyses indicate that simvastatin reduced the risk of fatal plus non-fatal cerebrovascular events (stroke and transient ischemic attacks) by 28% (75 patients vs 102 patients). Following the same kind of analyses, in hypercholesterolemic patients with diabetes mellitus, the risk of major coronary events was reduced by 55% (24 patients vs 44 patients). There was no statistically significant difference between groups in non-cardiovascular mortality. Simvastatin reduced the risk of major coronary events to a similar extent across the range of baseline total and LDL cholesterol levels. The risk of death in patients ≥60 years of age was decreased by 27% and in patients <60 years of age by 37% (p<0.01 in both age groups).

Figure 1

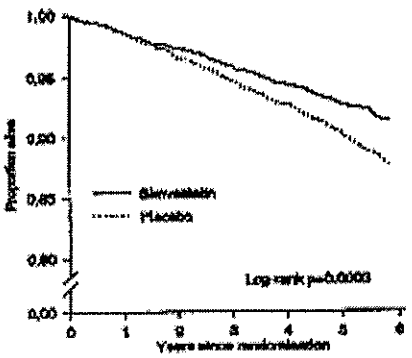
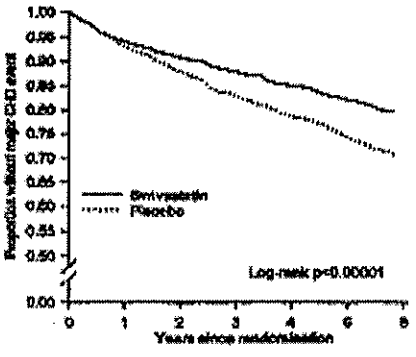


Figure 2



The 4S study excluded patients with familial hypercholesterolemia (FH) or with congestive heart failure. It is not established to what extent the findings of the 4S study can be extrapolated to these subpopulations of hypercholesterolemic patients.

- In patients with heterozygous FH optimal reduction in total and LDL-cholesterol necessitates a combination drug therapy in the majority of patients (see BIBLIOGRAPHY).

- Among patients who developed symptoms of heart failure during the 4S study, trends in reduced mortality (19% lower with simvastatin treatment compared to placebo), with reductions of similar magnitude in numbers of patients with major coronary events and numbers of major coronary events were consistent between this group and the total study cohort.

Because there were only 57 deaths among the patients with angina alone at baseline and 53 deaths among female patients, the effect of simvastatin on mortality in these subgroups could not be adequately assessed. However, trends in reduced coronary mortality and in major coronary events were consistent between these subgroups and the total study cohort.

In the Multicenter Anti-Atheroma Study, the effect of therapy with simvastatin on coronary atherosclerosis was assessed by quantitative coronary angiography in hypercholesterolemic men and women with coronary heart disease. In this randomized, double-blind, controlled clinical study, 404 patients with total cholesterol values of 212 to 308 mg/dL (5.5 to 8.0 mmol/L) and a mean baseline LDL value of 170 mg/dL (4.4 mmol/L) were treated with conventional measures and with simvastatin 20 mg/day or placebo. Angiograms were evaluated at baseline, two and four years. A total of 347 patients had a baseline angiogram and at least one follow-up angiogram. In the patients who received placebo, coronary atherosclerotic lesions worsened in a

near-linear manner. In contrast, simvastatin significantly slowed the progression of lesions as measured in the final angiogram by the mean change per-patient in minimum (p=0.005) and mean (p=0.026) lumen diameters (co-primary endpoints, indicating focal and diffuse disease, respectively), as well as in percent diameter stenosis (p=0.003). Simvastatin also significantly decreased the proportion of patients with new lesions (13% simvastatin vs 24% placebo, p=0.009) and with new total occlusions (5% vs 11 %, p=0.04). The mean change per-patient in mean and minimum lumen diameters calculated by comparing angiograms in the subset of 274 patients who had matched angiographic projections at baseline, two and four years is presented below (Figures 3 and 4).

Figure 3

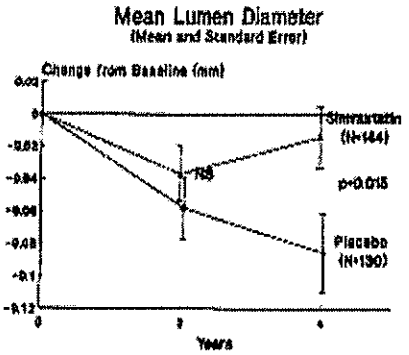
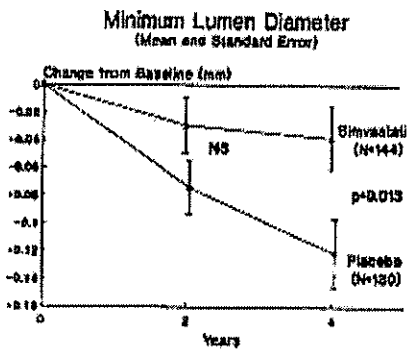


Figure 4



The Multicenter Anti-Atheroma Study, however, excluded patients with heterozygous familial hypercholesterolemia (FH). It is not clear to what extent these findings can be extrapolated to the familial hypercholesterolemic subpopulation not studied.

Animal Pharmacology

Cell Culture

Two systems have been utilized to demonstrate that simvastatin is an inhibitor of cholesterol synthesis; mammalian cells grown in culture and *in vivo* in the rat. The IC_{50} values for inhibition of sterol synthesis in cultured animal cells by simvastatin, and determined by measuring the incorporation of ^{14}C-acetate into ^{14}C-sterol, are 19.3 nM for mouse L-M cells, 13.3 nM for the rat hepatoma cell line H4IIE and 15.6 nM for the human hepatoma cell line Hep G-2. These results demonstrate that simvastatin is active against the human enzyme as well as the rodent one.

Rats

The inhibition of incorporation of ^{14}C-acetate into ^{14}C-cholesterol in rats has been used to assess the *in vivo* effectiveness of simvastatin.

Groups of ten male rats were given a single oral dose (administered by stomach tube) of simvastatin at doses ranging from 0.15 to 2.4 mg/kg. In this study, it was demonstrated that simvastatin is an orally active inhibitor of cholesterol synthesis with an ID_{50} value of less than 0.15 to 0.2 mg/kg and that 87% inhibition occurs within one hour after an oral dose of 2.4 mg/kg of the drug.

Dogs

Studies have been carried out in the dog in order to assess the effects of simvastatin on serum total lipoprotein cholesterol. This animal model has been shown to respond to HMG-CoA reductase inhibitors with respect to lowering of circulating cholesterol as opposed to rats, which show no sustained effects of these agents on cholesterol levels.

Male beagle dogs were treated with 12 g of cholestyramine, a bile acid sequestrant. Total plasma cholesterol was decreased by an average of 35%.

Five of these cholestyramine primed dogs received 1 mg/kg/day p.o. of simvastatin in their diet for a period of 21 days and 4 other cholestyramine primed dogs received 2 mg/kg/day p.o. of simvastatin in their diet for a period of 24 days. Treatment of these dogs resulted in an additional 29.1% and 37.6% decrease in total cholesterol, respectively) from the baseline established with cholestyramine.

The effects of simvastatin are primarily on LDL-cholesterol in spite of the fact that approximately 70-80% of circulating cholesterol in the dog is in the form of HDL-cholesterol. In the cholestyramine-primed dogs, LDL-cholesterol decreased by 57-72% with a 19-38% decrease in HDL-cholesterol.

In another study, five chow-fed dogs received 8 mg/kg/day p.o. of simvastatin in their diet for a period of 24 days. Total cholesterol and LDL-cholesterol decreased by an average of 26.2% and 62% respectively. HDL-cholesterol levels decreased slightly but the decrease was not considered significant.

Pharmacokinetics

The pharmacokinetic profile of simvastatin has been investigated in mice, rats and dogs.

Absorption of simvastatin, estimated relative to an intravenous reference dose, in rats and dogs, averaged about 85% of an oral dose. Studies in the dog have indicated that the availability of the absorbed drug to the general circulation is limited by extensive first-pass extraction in the liver, its

primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of simvastatin, the availability of drug to the general circulation is low.

In dogs, simvastatin and its active metabolite are > 90% bound to plasma protein.

Only in mice and rats is there evidence that a metabolite of simvastatin is formed by ß-oxidation. Biliary excretion is the major route of elimination of the metabolites of simvastatin.

In dogs, 74% of the radioactivity of an oral dose of ^{14}C-simvastatin was recovered in the feces and 11% in the urine.

TOXICOLOGY

Acute Toxicity

Simvastatin			
Species	**Sex**	**Route**	**LD_{50} (mg/kg)**
Mouse	Female	Oral	4411
Mouse	Male	Oral	3000
Mouse	Female	Intraperitoneal	798
Mouse	Male	Intraperitoneal	1033
Mouse	Female	Subcutaneous	1800
Mouse	Male	Subcutaneous	1009
Rat	Female	Oral	>5000
Rat	Male	Oral	4438
Rat	Female	Intraperitoneal	705
Rat	Male	Intraperitoneal	898
Rat	Female	Subcutaneous	672
Rat	Male	Subcutaneous	1088
Dog	F/M	Oral	>5000
Dihydroxy Open Acid form of Simvastatin L-654, 969			
Mouse	Female	Oral	1820
Mouse	Male	Oral	1625
Rat	Female	Oral	1280
Rat	Male	Oral	2080

Subacute and Chronic Toxicity Studies

The spectrum of effects produced by simvastatin in dogs, rats, mice, rabbits and monkeys shown on Table VII below is not unexpected in view of the magnitude of the dosage levels employed, the potency of simvastatin in inhibiting mevalonate synthesis and the essential role of the HMG-CoA reductase in maintaining cellular homeostasis.

TABLE VII: Simvastatin Target Organs Observed In Animal Studies					
	Species Affected				
	Dog	**Rat**	**Mouse**	**Rabbit**	**Monkey**
Liver	+	+	-	+	-
Thyroid	-	+	-	NT	-
Kidney	-	-	-	+	-
Gallbladder	-	N/A	-	+	-
Eye (lens)	+	+	-	-	-
Stomach (non-glandular)	N/A	+	+	N/A	N/A
Testis	+	-	-	-	-

NT = Not tested

NA = Not applicable

+ = Organ affected in some way by drug treatment

- = No effect observed in this organ in this species

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

TABLE VIII: Simvastatin Significant Adverse Changes		
	Minimal Toxic Dose (mg/kg/day)	**No-Effect Dose (mg/kg/day)**
DOGS		
Cataracts	50	10
Testicular degeneration	10	3
Elevated serum transaminase	2	ND
RABBITS		
Hepatocellular necrosis	50	30
Renal tubular necrosis	50	30
Gallbladder necrosis	90	50
RATS		
Hepatocellular atypia	25	5
Nonglandular gastric mucosal hyperplasia	1	ND
Thyroid follicular cell adenoma (females only)	25	5
Hepatomegaly (females only)	25	5
Posterior subcapsular or complete cataracts	120	90
MICE		
Nonglandular gastric mucosal hyperplasia	1	ND
Liver		
– hepatocellular adenoma	100	25
– hepatocellular carcinoma	100	25
Lung		
– adenoma	100	25

ND = Not Determined.

Several 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 assessments.

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

TABLE IX: Simvastatin

Key Issues Identified in Safety Assessment - Relationship to Inhibition of HMG-CoA Reductase

Clearly Mechanism Based

- Hepatic histomorphologic changes in rats.
- Hepatic renal and gallbladder necrosis in rabbits.
- Hyperplasia of the gastric nonglandular mucosa in rodents.

Probably Mechanism Based

- Serum transaminase elevations in dogs.
- Cataracts in dogs.

Relationship to Mechanism of Action Uncertain or Unknown

- Testicular degeneration in dogs.

Not Related to Inhibition of HMG-CoA Reductase

- Hepatomegaly and thyroid enlargement in rats.
- Thyroid follicular cell adenomas in rats.

Cataracts have been detected at high doses in dog studies with simvastatin, although at a very low incidence. While there is no clear correlation between the magnitude of serum lipid-lowering and the development of cataracts, a consistent relationship has been observed between high serum levels of drug and cataract development with simvastatin and related HMG-CoA reductase inhibitors. Serum levels (expressed as total inhibitors) in dogs receiving the minimally cataractogenic dose of simvastatin of 50 mg/kg/day are 21 times higher than those in man receiving the maximally anticipated therapeutic dose of 0.8 mg/kg (based on a 50 kg human dose). The no-effect dose of simvastatin for cataracts is 10 mg/kg/day. This dose was administered to dogs for a period of up to 2 years without the production of opacities.

Mild, transient dose-related increases in serum transaminases have been observed in dogs receiving simvastatin. These occurred either as chronic low level elevations or as transient enzyme spikes in approximately 10-40% of the dogs receiving this drug and resolved despite continued drug administration. None of the dogs experiencing these transaminase elevations

demonstrated any symptoms of illness; and none of the transaminase elevations have progressed to levels associated with frank hepatic necrosis, despite continued drug administration. No histopathological changes have been identified in the liver of any dogs receiving simvastatin.

Testicular degeneration has been seen in two dog safety studies with simvastatin, at doses of 30 and 90 mg/kg/day. Special studies designed to further define the nature of these changes have not met with success since the effects are poorly reproducible and unrelated to dose, serum cholesterol levels, or duration of treatment. Furthermore, no changes in serum androgens or gonadotropins have been related to simvastatin treatment in dogs. Simvastatin has been administered for up to 2 years to dogs at a dose of 50 mg/kg/day without any testicular effects.

Skeletal muscle necrosis was seen in one study in rats given 90 mg/kg b.i.d., but this was a lethal dosage in rats.

Carcinogenesis and Mutagenesis Studies

Initial carcinogenicity studies conducted in rats and mice with simvastatin employed doses ranging from 1 mg/kg/day to 25 mg/kg/day (31 times the maximum recommended human dose)*. No evidence of a treatment-related incidence of tumor types was found in mice in any tissue.

A statistically significant ($p \leq 0.05$) increase in the incidence of thyroid follicular cell adenomas was observed in female rats receiving 25 mg/kg/day of simvastatin (31 times the maximum recommended human dose). This benign tumor type was limited to female rats; no similar changes were observed in male rats or in female rats at lower dosages [(up to 5 mg/kg/day) 6.25

* Based on 50 kg human being.

times the maximum recommended human dose]. These tumors are a secondary effect reflective of a simvastatin mediated enhancement of thyroxine clearance in the female rat. No other statistically significant increased incidence of tumor types was identified in any tissues in rats receiving simvastatin.

Results of an additional 73-week carcinogenicity study in mice receiving simvastatin doses up to 400 mg/kg/day (500 times the maximum recommended human dose, based on a 50 kg person) exhibited increased incidences of hepatocellular adenomas and carcinomas, and pulmonary adenomas at doses of 100 and 400 mg/kg/day, and an increase in the incidence of harderian gland adenomas at 400 mg/kg/day. A no-effect dose of 25 mg/kg/day (31 times the maximum recommended human dose) was established in this study and from the results of the initial 92-week carcinogenicity study in mice.

Results of an additional 106-week carcinogenicity study in rats receiving simvastatin doses ranging from 50 mg/kg/day to 100 mg/kg/day (62.5 to 125 times the maximum recommended human dose) exhibited a treatment-related increase in the incidence of hepatocellular neoplasms. The no-effect dose remains at 25 mg/kg/day (31 times the maximum recommended human dose) as established in the initial carcinogenicity study. An increase in the incidence of thyroid hyperplastic lesions was also observed; however, this is consistent with the previous finding that this is a species-specific response and has no implications for man.

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 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

There was no evidence of a teratogenic effect in rats or rabbits at maximally tolerated doses of up to 25 mg/kg/day or 10 mg/kg/day, respectively (31 and 12.5 times the maximum recommended human dose, respectively).

However, in rats, an oral dose of 60 mg/kg/day of the hydroxy acid, pharmacologically active metabolite of simvastatin resulted in decreased maternal body weight and an increased incidence of fetal resorptions and skeletal malformations compared with controls. Subsequent studies conducted at dosages of up to 60 mg/kg/day with this metabolite showed that these resorptions and skeletal malformations were consequences of maternal toxicity (forestomach lesions associated with maternal weight loss) specific to rodents and are highly unlikely to be due to a direct effect on the developing fetus. Although no studies have been conducted with simvastatin, maternal treatment of pregnant rats with a closely related HMG-CoA reductase inhibitor at dosages of 80 and 400 mg/kg/day (10- and 52-fold the maximum recommended therapeutic dose based on mg/m^2 body surface area) has been shown to reduce the fetal plasma levels of mevalonate.

BIBLIOGRAPHY

1. Alberts AW. HMG-CoA reductase inhibitors -- the development. In: Stokes IIIJ, Mancini M, eds. Atherosclerosis Reviews. Vol.18. New York Raven Press, 1988; 123-31.

2. Barbir M, Rose M, Kushwaha S, et al. Low-dose simvastatin for the treatment of hypercholesterolemia in recipients of cardiac transplantation. Int J Cardiol 1991; 33: 241-6.

3. Castelli W. Epidemiology of coronary heart disease: the Framingham study. Am J Med 1984; 76: 4-12.

4. Chaudron JM, Luwaert R. Effects of simvastatin on plasma lipids in coronary patients with severe hypercholesterolaemia. Acta Cardiol 1989; 44: 48-49.

5. Daniels H, Holvoet G, Stroobandt R. Effects of simvastatin in plasma lipids in patients with hypercholesterolemia. Acta Cardiol 1989; 44: 49-50.

6. Davidson MH, Stein EA, Dujovne CA, et al. The efficacy and six-week tolerability of simvastatin 80 and 160 mg/day. Am J Cardiol 1997; 79: 38-42.

7. Erkelens DW, Baggen MG, Van Doormaal JJ, et al. Clinical experience with simvastatin compared with colestyramine. Drugs 1988; 36(Suppl 3): 87-92.

8. Frohlich J, Fodor G, McPherson R, et al. Rationale for and outline of the recommendations of the Working Group on Hypercholesterolemia and Other Dyslipidemias: Interim report. Can J Cardiol 1998; 14(Suppl A): 17A-21A.

9. Germershausen JI, Hunt VM, Bostedor RG, et al. Tissue selectivity of the cholesterol-lowering agents lovastatin, simvastatin and pravastatin in rats *in vivo.* Biochem Biophys Res Commun 1989; 158: 667-75.

10. Gerson RJ, MacDonald JS, Alberts AW, et al. Animal safety and toxicology of simvastatin and related hydroxy-methylglutaryl-coenzyme A reductase inhibitors. Am J Med 1989; 87(Suppl 4A): 28S-38S.

11. Ghirlanda 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: 226-9.

12. Grundy S. Dietary and drug regulation of cholesterol metabolism in man. In: Paoletti R, Glueck C, eds. Lipid Pharmacology. Vol. II. New York, Academic, 1976; 127-59.

13. Grundy SM. HMG-CoA reductase inhibitors for treatment of hypercholesterolemia. N Engl J Med 1988; 319: 24-33.

14. Helve E, Ojala JP, Tikkanen MJ. Simvastatin and gemfibrozil in the treatment of primary hypercholesterolemia. J Appl Cardiol 1988; 3: 381-8.

15. Horlick L, Lupien P, Beare-Rogers J, et al. Canadian Consensus Conference on Cholesterol. Preliminary Report, Ottawa, Ontario, March 9-11, 1988.

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

17. Kjekshus J, Pederson TR, Olsson AG, et al. The effects of simvastatin on the incidence of heart failure in patients with coronary heart disease. J Card Fail 1997; 3: 249-54.

18. Knops RE, Kroon AA Mol MJTM, et al. Long-term experience (6 years) with simvastatin in patients with heterozygous familial hypercholesterolemia. Netherlands J Med 1995; 46: 171-8.

19. Laaksonen R, Ojala JP, Tikkanen MJ, Himberg JJ. Serum ubiquinone concentrations after short- and long-term treatment with HMG-CoA reductase inhibitors. Eur J Clin Pharmacol 1994; 46: 313-7.

20. MAAS Investigators. Effect of simvastatin on coronary atheroma: the Multicenter Anti-Atheroma Study (MAAS). Lancet 1994;344:633-8.

21. Mauro VF. Clinical pharmacokinetics and practical applications of simvastatin. Clin Pharmacokinet 1993; 24(3): 195-202.

22. Meier C, Stey C, Brack T, et al. Rhabdomyolysis in patients treated with simvastatin and cyclosporin: role of hepatic cytochrome P 450 system activity. Schweiz Med Wochenschr 1995; 25: 1342-6.

23. Miettinen TA, Pyörälä K, Olsson AG, et al. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris: Findings from the Scandinavian Simvastatin Survival Study (4S). Circulation I997; 96(12): 4211-8.

24. Mol MJTM, Erkelens DW, et al. Effects of synvinolin (MK-733) on plasma lipids in familial hypercholesterolaemia. Lancet 1986; II(8513): 936-9.

25. Pederson TR, Berg K, Cook TJ, et al. Safety and tolerability of cholesterol lowering with simvastation during 5 years in the Scandinavian Simvastatin Survival Study. Arch Intern Med 1996; 156: 2085-92.

26. Pederson TR, Kjekshus J, Pyörälä K, et al. Effect of simvastatin on ischemic signs and symptoms in the Scandinavian Simvastatin Survival Study (4S). Am J Cardiol 1998; 81: 333-5.

27. Phan T, McLeod JG, Pollard JD, et al. Peripheral neuropathy associated with simvastatin. J Neurol Neurosurg Psychiatry 1995; 58: 625-8.

28. Pyörälä K, Pedersen TR, Kjekshus J, et al. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. Diabetes Care 1997; 20(4): 614-20.

29. Quérin S, Lambert R, Cusson JR, et al. Single-dose pharmacokinetics of ^{14}C-lovastatin in chronic renal failure. Clin Pharmacol Ther 1991; 50: 437-41.

30. Rabelink AJ, Hene RJ, Erkelens DW, et al. Effects of simvastatin and cholestyramine on lipoprotein profile in hyperlipidaemia of nephrotic syndrome. Lancet 1988; II(8624): 1335-8.

31. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383-9.

32. Seed M, Hoppichler F, Reaveley D, et al. Relation of serum lipoprotein(a) concentration and apolipoprotein(a) phenotype to coronary heart disease in patients with familial hypercholesterolemia. N Engl J Med 1990; 322: 1494-9.

33. Slater EE, MacDonald JS. Mechanism of action and biological profile of HMG-CoA reductase inhibitors: a new therapeutic alternative. Drugs 1988; 36(Suppl 3): 72-82.

34. Stalenhoef AF, Mol MJT, Stuyt PMJ. Efficacy and tolerability of simvastatin (MK-733). Am J Med 1989; 87(Suppl 4A): 39S-43S.

35. Stein EA. Treatment of familial hypercholesterolemia with drugs in children. Arteriosclerosis 1989; 9 (Suppl I):I-145 - I-151.

36. Stein E, Kreisberg R, Miller V, et al. Effects of simvastatin and cholestyramine in familial and non-familial hypercholesterolemia. Arch Int Med I990; 150: 341-5.

37. Summary of the Second Report of the National Cholesterol EducationProgram (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). JAMA 1993; 269: 3015-23.

38. Tikkanen MJ, Bocanegra TS, Walker JF, Cook T. Comparison of low-dose simvastatin and gemfibrozil in the treatment of elevated plasma cholesterol. A multicenter study. Am J Med 1989; 87(Suppl 4A): 47S-53S.

39. Tobert JA. New developments in lipid-lowering therapy: the role of inhibitors of hydroxymethylglutaryl-coenzyme A reductase. Circulation 1987; 76: 534-8.

40. Tobert JA, Leslie BR, Schaefer EJ, et al. HMG-CoA reductase inhibitors for hypercholesterolemia. N Engl J Med 1988; 319: 1222-3.

41. Uauy R, Vega GL, Grundy SM, Bilheimer DW. Lovastatin therapy in receptor-negative homozygous familial hypercholesterolemia: lack of effect on low-density lipoprotein concentrations or turnover. J Pediatr 1988; 113: 387-92.

42. Volpe R, Arca M, Ginnetti MG, et al. The efficacy and safety of pravastatin and simvastatin in patients with primary hypercholesterolemia. Curr Ther Res 1992; 51 (3): 422-30.

43. Walker JF. Simvastatin: the clinical profile. Am J Med 1989; 87(Suppl 4A): 44S-46S.