PRODUCT MONOGRAPH

[Pr] ratio-SIMVASTATIN

Simvastatin Tablets USP

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

Lipid Metabolism Regulator

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 5 mg, 10 mg, 20 mg, 40 mg and 80 mg	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

In patients at high risk of coronary events, because of existing Coronary Heart Disease (CHD) or other occlusive arterial disease, or being over the age of 40 years with a diagnosis of diabetes, **ratio-SIMVASTATIN** (simvastatin) is indicated to:

- reduce the risk of total mortality, by reducing CHD deaths;
- reduce the risk of myocardial infarction;
- reduce the risk of ischemic stroke.

This indication applies to patients at high risk of coronary events, regardless of lipid status.

In hypercholesterolemic patients with coronary heart disease, **ratio-SIMVASTATIN** (simvastatin) slows the progression of coronary atherosclerosis, including reducing the development of new lesions and new total occlusions.

Hyperlipidemia

ratio-SIMVASTATIN (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

[†] 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 EngI J Med 1967;276:148-56.

cholesterol (19-36%), LDL-cholesterol (26-47%), apolipoprotein B (19-38%), and triglycerides (12- 33%), in patients with mild to severe hyperlipidemia (Fredrickson Types IIa and IIb). Simvastatin also raises HDL-cholesterol (8- 16%) 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%), respectively. One patient with absent LDL-cholesterol receptor function had an LDL-cholesterol reduction of 41% with the 80 mg/day dose (see CLINICAL TRIALS).

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.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Active liver disease or unexplained persistent elevations of serum transaminases.
- Pregnancy and lactation (see WARNINGS AND PRECAUTIONS, Pregnant Women and Nursing Women.

WARNINGS AND PRECAUTIONS

[††] DeLong DM, et al. A comparison of methods. JAMA 1986;256:2372-7.

Clinically significant warnings and precautions are listed in alphabetical order.

General

Before instituting therapy with **ratio-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 ratio-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.

Endocrine and Metabolism

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 REFERENCES).

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 **ratio-SIMVASTATIN**.

Endocrine: 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, Overview).

Hepatic/Biliary/Pancreatic

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 (4S) (see CLINICAL TRIALS), 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.

In HPS (Heart Protection Study) (See CLINICAL TRIALS), in which 20,536 patients were randomized to receive simvastatin 40 mg/day or placebo, the incidences of elevated transaminases (> 3X ULN confirmed by repeat test) were 0.21% (n=21) for patients treated with simvastatin and 0.09% (n=9) for patients treated with placebo.

It is recommended that liver function tests be performed at baseline and thereafter when clinically indicated. Patients titrated to the 80 mg dose should receive an additional test at prior to titration, 3 months after titration to the 80 mg dose, and periodically thereafter (e.g., semiannually) for the first year of treatment. 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 **ratio-SIMVASTATIN** (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.

Muscular

Myopathy/Rhabdomylysis: 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/Rambdomyolysis Caused by Drug Interactions

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 WARNINGS AND PRECAUTIONS, Myopathy/Rhabdomyolysis and DRUG INTERACTIONS, General).

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

- **Potent inhibitors of CYP3A4: e.g., the antifungal azoles itraconazole, and ketoconazole, the antibiotics erythromycin, clarithromycin and telithromycin, HIV protease inhibitors, or the antidepressant nefazodone, particularly with higher doses of simvastatin** (see DRUG INTERACTIONS and DETAILED PHARMACOLOGY, Pharmacokinetics).

Other drugs:

- **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 DRUG INTERACTIONS and DETAILED PHARMACOLOGY, Pharmacokinetics).

- **Cyclosporine** particularly with higher doses of simvastatin (see DRUG INTERACTIONS and DETAILED PHARMACOLOGY, Pharmacokinetics).

- **Amiodarone or verapamil with higher doses of simvastatin** (see DRUG INTERACTIONS). In an ongoing clinical trial, myopathy has been reported in 6% of patients receiving simvastatin 80 mg and amiodarone.

- **Diltiazem:** Patients on diltiazem treated concomitantly with simvastatin 80 mg have a slightly increased risk of myopathy. The risk of myopathy is approximately 1% in these patients. In clinical studies, the risk of myopathy in patients taking simvastatin 40 mg with diltiazem was similar to that in patients taking simvastatin 40 mg without dilitiazem (see 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 potent CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, 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 labelled 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 gemfibrozil should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination. The benefits of the use of simvastatin in patients receiving other fibrates, niacin or cyclosporine should be carefully weighed against the risks of these drug combinations. 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 clinical benefit is likely to outweigh the increased risk of myopathy.

Ophthalmologic

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

Renal

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 AND PRECAUTIONS, Myopathy/Rhabdomyolysis).

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 AND PRECAUTIONS, Myopathy/Rhabdomyolysis and DRUG INTERACTIONS).**

Skin

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

Special Populations

Pregnant Women: ratio-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, **ratio-SIMVASTATIN** should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with **ratio-SIMVASTATIN** should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant. (See CONTRAINDICATIONS and REFERENCES).

Nursing Women: 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 **ratio-SIMVASTATIN** should not nurse (see CONTRAINDICATIONS).

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

Geriatrics (> 65 years of age): 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.

Higher dosage (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 elderly or are concomitantly administered P-450 inhibitors (see WARNINGS AND PRECAUTIONS, Myopathy/Rhabdomyolysis and DRUG INTERACTIONS).**

Monitoring and Laboratory Tests

In the differential diagnosis of chest pain in a patient on therapy with simvastatin, cardiac and noncardiac fractions of serum transaminase and creatine phosphokinase levels should be determined.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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 DETAILED PHARMACOLOGY, 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: See WARNINGS AND PRECAUTIONS, Ophatlmologic.

Laboratory Tests: Marked persistent increases of serum transaminases (ALT, AST) have been noted (see WARNINGS AND PRECAUTIONS).

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 AND PRECAUTIONS, Myopathy/Rhabdomyolysis and DRUG INTERACTIONS, Drug/Laboratory Interactions).

Uncontrolled Clinical Studies or Post-Market Adverse Drug Reactions

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.

Gastrointestinal:
Vomiting

Hematologic:
Anemia
Leukopenia
Purpura

Hepatic/Pancreatic:
Hepatitis
Jaundice
Pancreatitis

Laboratory Test
Elevated alkaline phosphatase and y-glutamyl transpeptidase have been reported.

Muscular:
Rhabdomyolysis
Muscle Cramps
Myalgia

Neurologic:
Dizziness
Paresthesia
Peripheral Neuropathy
Peripheral neuropathy with muscle weakness or sensory disturbance has been reported (see REFERENCES).

Psychiatric:
Depression

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

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

Skin:
Erythema Multiforme including Stevens-Johnson Syndrome
Rash
Pruritus
Alopecia

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.

DRUG INTERACTIONS

Overview

Simvastatin has no CYP3A4 inhibitory activity; therefore, it is not expected to affect plasma levels of other drugs metabolized by CYP3A4 (see DETAILED 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 itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, and nefazodone (see WARNINGS AND PRECAUTIONS, Myopathy/Rhabdomyolysis Caused by Drug Interactions).

Drug-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 (Cholestyramine): 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 (≥1 g/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 AND PRECAUTIONS, Myopathy/Rhabdomyolysis Caused by Drug Interactions). There is no evidence to suggest that these agents affect the pharmacokinetics of simvastatin.

Myopathy, including rhabdomyolysis, has occured 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 AND PRECAUTIONS, Myopathy/Rhabdomyolysis Caused by Drug Interactions).

Erythromycin, Clarithromycin and Telithromycin: See WARNINGS AND PRECAUTIONS, 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.

Cyclosporine: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine with higher doses of simvastatin (see WARNINGS AND PRECAUTIONS, 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 AND PRECAUTIONS, 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.

Diltiazem: Patients on diltiazem treated concomitantly with simvastatin 80 mg have a slightly increased risk of myopathy. The risk of myopathy is approximately 1% in these patients. In clinical studies, the risk of myopathy in patients taking simvastatin 40 mg with diltiazem was similar to that in patients without diltiazem (see WARNINGS AND PRECAUTIONS, Myopathy/Rhabdomyolysis Caused by Drug Interactions).

Verapamil: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of verapamil with higher doses of simvastatin (see WARNINGS AND PRECAUTIONS, 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-Food 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 AND PRECAUTIONS, Myopathy/Rhabdomyolysis Caused by Drug Interactions).

Drug-Laboratory Interactions

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

- If appropriate, a program of weight control and physical exercise should be implemented.
- **Patients at high risk of coronary events, because of existing Coronary Heart Disease (CHD) or other occlusive arterial disease, or being over the age of 40 years with a diagnosis of diabetes:** The usual starting dose of **ratio-SIMVASTATIN** (simvastatin) is 40 mg/day given as a single dose in the evening. Drug therapy can be initiated simultaneously with diet or exercise.

- **Patients with Hyperlipidemia (who are not in the risk categories above):** The patient should be placed on a standard cholesterol-lowering diet before receiving **ratio-SIMVASTATIN** (simvastatin) and should continue on this diet during treatment with **ratio-SIMVASTATIN** (simvastatin). The usual starting dose is 10 mg/day given as a single dose in the evening. Patients who require a large induction in LDL-C (more than 45%) may be started at 40 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 **ratio-SIMVASTATIN** (simvastatin). Adjustments of dosage, if required, should be made as specified above.

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

- **Concomitant Therapy:** (See DRUG INTERACTIONS, Concomitant Therapy with other Lipid Metabolism Regulators.)

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

Recommended Dose and Dosage Adjustment

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. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80 mg/day given as a single dose in the evening.

Missed dose

If a tablet is missed at its usual time, it should be taken as soon as possible. But, if it is too close to the time of your next dose: only the prescribed dose should be taken at the appointed time. **A double dose should not be taken.**

OVERDOSAGE

A few cases of overdosage have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae.

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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

ratio-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.

Pharmacodynamics

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.

Pharmacokinetics

Simvastatin has complex pharmacokinetic characteristics (see DETAILED PHARMACOLOGY).

Metabolism: 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 DETAILED PHARMACOLOGY, Pharmacokinetics).

STORAGE AND STABILITY

ratio-SIMVASTATIN (simvastatin) should be stored at room temperature (15°C - 30°C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

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

ratio-SIMVASTATIN 10 mg tablets: each light pink, shield-shaped, biconvex, straight-edged, film-coated tablet, engraved "rph" on one side and 10 on the other, contains 10 mg simvastatin. Available in bottles of 100 and 500, and blisters of 30.

ratio-SIMVASTATIN 20 mg tablets: each peach, shield-shaped, biconvex, straight-edged, film-coated tablet, engraved "rph" on one side and 20 on the other, contains 20 mg simvastatin. Available in bottles of 100, 250 and 500, and blisters of 30.

ratio-SIMVASTATIN 40 mg tablets: each dusty rose, shield-shaped, biconvex, straight-edged, film-coated tablet, engraved "rph" on one side and 40 on the other, contains 40 mg simvastatin. Available in bottles of 100 and 500, and blisters of 30.

ratio-SIMVASTATIN 80 mg tablets: each dusty rose, capsule-shaped, biconvex, straight-edged, film-coated tablet, engraved "rph" on one side and 80 on the other, contains 80 mg simvastatin. Available in bottles of 100, and blisters of 30.

Non-medicinal ingredients: colloidal silicon dioxide, crospovidone, hydroxyethyl cellulose, microcrystalline cellulose, polyethylene glycol, titanium dioxide and zinc stearate.

ratio-SIMVASTATIN 5 mg and 10 mg tablets contain yellow ferric oxide.
ratio-SIMVASTATIN 10 mg, 20 mg, 40 mg and 80 mg tablets also contain red ferric oxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

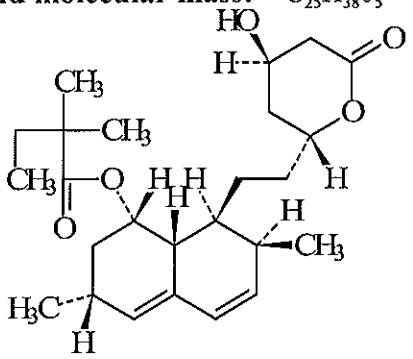
Drug Substance

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-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl 2,2- dimethylbutanoate.

Molecular formula and molecular mass: $C_{25}H_{38}O_5$ and 418.58

Structural formula:



Physicochemical properties:

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.

CLINICAL TRIALS

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 1), 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 (TG), and slightly increased HDL-cholesterol (HDL-C).

TABLE 1

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)	TG (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 and combined (mixed) hyperlipidemia are presented in Table 2:

TABLE 2

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)	TG (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
Multicenter Combined Hyperlipidemia Stu						
Placebo		125	1	2	3	-4
Simvastatin	**- 40 mg***	123	-25	-29	13	-28
	- 80 mg*	124	-31	-36	16	-33

* 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

$\leq$ 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.

The results of subgroup analyses from two studies including patients with Frederickson type IV hyperlipidemia are presented in Table 2. Both studies were double blind and placebo controlled; one was a crossover study and included placebo or simvastatin 40 and 80 mg/day and the other was a parallel study and included placebo or simvastatin 40 and 80 mg/day. Each treatment group included approximately 30 patients. The respective baseline values for the type IV patients in the 2 studies were: total-C = 279 (7.23) and 233 mg/dL (6.04 mmol/L); LDL-C = 120 (3.11) and 100 (2.59); HDL-C = 37 (0.96) and 35 (0.91); TG = 435 (4.93) and 441 (5.01); VLDL-C = 99 (2.56) and 94 (2.44); non-HDL-C = 243 (6.29) and 198 (5.13).

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 3.

TABLE 3

Simvastatin in FH and NON-FH Patients

(Percent Change From baseline after 12 weeks)

	TOTAL CHOLESTEOL 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 REFERENCES).

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 4,5,6.

TABLE 4

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)	TG (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 5

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

TABLE 6

Simvastatin vs. Gemfibrozil

(Percent change from Baseline After 12 Weeks)

TREATMENTS	N	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	VLDL-C (mean)	TG (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 (45), 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 MIwas 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

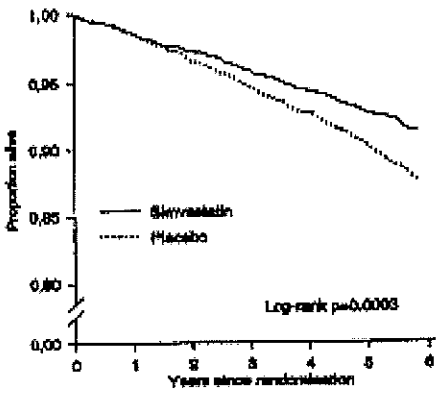
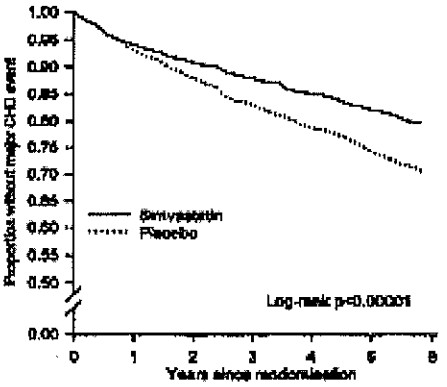


Figure 2



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 **REFERENCES**).

- 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.

The Heart Protection Study (HPS) was a large- multi-center, randomized, placebo-controlled, double-blind study with a mean duration of 5 years conducted in 20,536 patients (10,269 on simvastatin and 10,267 on placebo). Patients were 40-80 years of age (97% Caucasian) and at high risk of developing a major coronary event (i.e., patients with diabetes, history of stroke or other cerebrovascular disease, peripheral vessel disease, or with existing coronary heart disease). LDL-C levels were assayed using a direct method and collected without regard for meals (results are about 5% lower than fasting sample). At baseline, 3,421 patients (17%) had LDL-C levels below 2.6 mmol/L (100 mg/dL); 7,068 patients (34%) had levels between 2.6 and 3.4 mmol/L (100 mg/dL and 130 mg/dL); and 10,047 patients (49%) had levels greater than 3.4 mmol/L (130 mg/dL).

The HPS results showed that simvastatin 40 mg/day significantly reduced: total and CHD mortality; major coronary events (a composite endpoint comprised non-fatel MI or CHD deaths); stroke; and coronary revascularization procedures (see Table 7). Risk reductions of approximately one quarter were observed for major coronary events and stroke. These risk reductions are likely underestimates due to the fact that 33% of the patients in the intention-to-treat analysis did not comply with the study protocol (i.e., patient allocated placebo took a statin, or patients allocated simvastatin did not take the study drug).

TABLE 7

Summary of Results of HPS

Endpoint	Simvastatin (n=10,269) (%)	Placebo (n=10,267) (%)	Absolute Risk Reduction* (%) (95% CI)	Relative Risk Reduction (%) (95% CI)	P value
Primary					
Mortality	12.9	14.6	1.7 (0.8 - 2.7)	13 (6-19)	p=0.0003
CHD mortality	5.7	6.8	1.2 (0.5 - 1.8)	18 (8 - 26)	p=0.0005
Secondary					
Major coronary events† ‡	8.7	11.8	3.1 (2.2 - 3.9)	27 (21 - 33)	p<0.0001
Stroke	4.3	5.6	1.4 (0.8 - 2.0)	25 (15-34)	p<0.0001
Key Tertiary					
Coronary revascularization	4.9	7.0	2.1 (1.5 - 2.8)	30 (22-38)	p<0.0001

* Based on difference in crude events rates

† See Figure 3 (results by baseline characteristics)

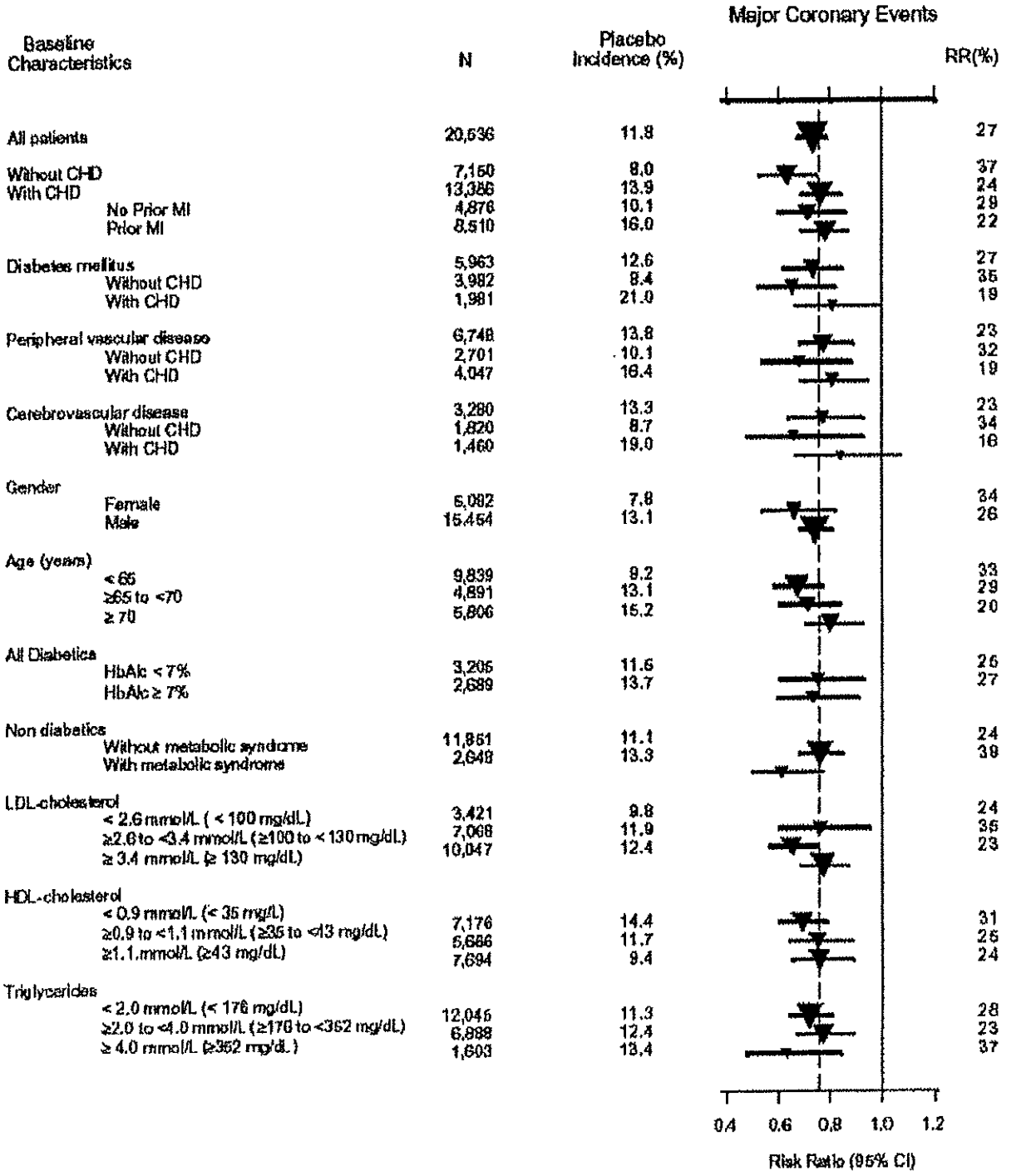
‡ A composite of non-fatal myocardial infraction or CHD deaths

The effects of simvastatin on major coronary events are shown below for selected subgroups of patients (see Figure 3).

Figure 3

The Beneficial Effects of Treatment with Simvastatin on Major Coronary Events in Heart Protection Study

N= number of patients in each subgroup. All subgroups were defined at baseline. Placebo incidence is the percentage of patients in the placebo group who had one or more Major Coronary Events during the study. The inverted triangles are points estimates of the risk ratio in the simvastatin group, with their 95% confidence intervals represented as a line. If the point estimate fell on the left of the unity line, the observed outcome was better in patients allocated active



simvastatin. Conversely, if it fell on the right, the observed outcome was better in patients allocated placebo. The areas of triangles are proportional to the number of patients with the relative endpoint. The vertical dashed line represents the

point estimate of relative risk in the entire study population. RR(%) represents risk reduction, i.e., (1 -risk ratio) X 100%.

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 4 and 5).

Figure 4

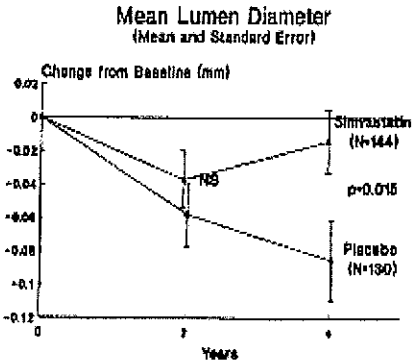
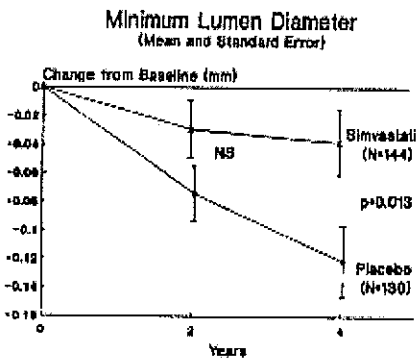


Figure 5



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

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 either ratio-SIMVASTATIN 80 mg tablets 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)

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	ratio-SIMVASTATIN	Zocor®†	
AUC_T (ng•hr/mL)	60.8 66.7 (41)	62.9 73.3 (58)	96.7
AUC_I (ng•hr/mL)	66.2 73.3 (44)	67.7 81.6 (66)	102.3
C_{max} (ng/mL)	11.1 12.8 (57)	12.9 15.1 (58)	85.9
T_{max} (hr)*	2.00 (111)	1.98 (66)	
$T_{1/2}$ (hr)*	7.28 (38)	6.55 (39)	

* Arithmetic means (CV%).

** Based on the least squares estimate.

† Zocor® is manufactured by Merck Frosst Canada Inc., and was purchased in Canada.

DETAILED 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 1-5 under CLINICAL TRIALS).

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 WARNINGS AND PRECAUTIONS Endocrine). 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 ß-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.

Although the mechanism is not fully understood, cyclosporine increases the AUC of simvastatin acid presumably due, in part, to inhibition by CYP3A4.

In a study of 12 healthy volunteers, simvastatin at the maximal 80-mg dose had no effect on the metabolism of the probe CYP3A4 substates 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 AND PRECAUTIONS, Myopathy/Rhabdomyolysis and DRUG INTERACTIONS).

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}Csterol, 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 8 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 8:

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 9:

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 10:

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 5 times higher than those in man receiving the maximally anticipated therapeutic dose of 1.6 mg/kg (based on 80 mg/day for a 50 kg person). 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 (16 times the maximum recommended human dose) [based on 50 kg person]. 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 (16 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) 3.1 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 250 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 16 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 to100 mg/kg/day (31 to 63 times the maximum recommended human dose) exhibited a treatment-related increase in the incidence of hepatocellular neoplasms. The a no-effect dose remains at 25 mg/kg/day (16 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 (16 and 6.3 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.

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PART III: CONSUMER INFORMATION

[Pr]ratio-SIMVASTATIN (simvastatin)

ratio-SIMVASTATIN Tablets

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

ratio-SIMVASTATIN is the brand name of ratiopharm 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 **ratio-SIMVASTATIN** to reduce the health risk associated with Coronary Heart Disease (CHD).

If you have CHD or other occlusive arterial disease (previous stroke, symptomatic peripheral vascular disease), or diabetes (regardless of the amount of cholesterol in your blood) ratio-SIMASTATIN should lessen the risk of heart attack or stroke. should lessen the risk of a heart attack or stroke.

ratio-SIMVASTATIN reduces the amount of cholesterol in your blood. Elevated cholesterol can cause CHD by clogging the blood vessels that carry oxygen and nutrients to the 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 tablets 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), pravastatin (Pravachol) or rosuvastatin (Crestor) - and were allergic, or reacted badly to it.
- You have a 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 **ratio-SIMVASTATIN**, stop taking it and contact your physician immediately.
- You are breast-feeding or intend to breast-feed.

TAKING ratio-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 **ratio-SIMVASTATIN**. You should also tell any physician who is prescribing a new medication for you that you are taking **ratio-SIMVASTATIN**.

Because taking **ratio-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 you physician if you are taking:

- cyclosporine (immunosuppressant)
- antifungal agents (such as itraconazole or ketoconazole)
- fibric acid derivatives (bezafibrate, fenofibrate and gemfibrozil) (drug to treat lipids problems)
- the antibiotics (erythromycin, clarithromycin and telithromycin)
- HIV protease inhibitors (such as indinavir, nelfinavir, ritonavir and saquinavir)
- the antidepressant nefazodone
- amiodarone (a drug used to treat an irregular heartbeat)
- verapamil or diltiazem (drugs used to treat high blood pressure, angina, or other heart conditions)
- 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 **ratio-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°C 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

Contact your physician promptly if you experience muscle pain, tenderness or weakness. This is because on rare occasions, muscle problems can be serious, including muscle breakdown resulting in kidney damage.

This risk of muscle breakdown is greater for patients taking higher doses of **ratio-SIMVASTATIN**. This risk of muscle breakdown is greater for patients with abnormal kidney function.

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 **ratio-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: colloidal silicon dioxide, crospovidone, hydroxyethyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, polyethylene glycol, titanium dioxide and zinc stearate.

ratio-SIMVASTATIN 5 mg and 20 mg tablets also contain yellow ferric oxide. **ratio-SIMVASTATIN** 10 mg, 20 mg, 40 mg and 80 mg tablets also contain red ferric oxide.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 1-866-234-2345
toll-free fax 1-866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
Canadian Adverse Drug Reaction
Monitoring Program
(CADRMP)
Health Canada
Address Locator : 0201C2
Ottawa, ON
K1A 1B9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional. This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting:

ratiopharm inc,.
17 800 Lapointe, Mirabel
Quebec, Canada, J7J 1P3
1-800-337-2584

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