

PRODUCT MONOGRAPH

PrSEPTA - SIMVASTATIN

Simvastatin Tablets, USP

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

Lipid Metabolism Regulator

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PrSEPTA-SIMVASTATIN
Simvastatin Tablets, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	ALL Non-medicinal Ingredients
oral	tablet 5 mg, 10 mg, 20 mg, 40 mg, 80 mg	Ascorbic acid, butylated hydroxyanisole, citric acid monohydrate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, talc, and titanium dioxide. Tablets 5 mg, 10 mg and 20 mg, 40mg and 80mg contain yellow ferric oxide. Tablets 10 mg, 20 mg, 40 mg and 80 mg also contain red ferric oxide.

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, SEPTA-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, SEPTA-SIMVASTATIN slows the progression of coronary atherosclerosis, including reducing the development of new lesions and new total occlusions.

Hyperlipidemia

SEPTA-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)¹, or combined (mixed) hyperlipidemia (Type IIb)¹ 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 (12-33%), 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 SEPTA-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:

$$\text{LDL-C (mmol/L)} = \text{Total cholesterol} - [(0.37 \times \text{triglycerides}) + \text{HDL-C}]^2$$

$$\text{LDL-C (mg/dL)} = \text{Total cholesterol} - [(0.16 \times \text{triglycerides}) + \text{HDL-C}]$$

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.

¹ A disorder of lipid metabolism characterized by elevated serum cholesterol levels in association with normal triglyceride levels (Type IIa) or with increased triglyceride levels (Type IIb). Fredrickson DS, Levy RI, Lees RS. Fat transport in lipoproteins - An integrated approach to mechanisms and disorders. *N Engl J Med* 1967;276:148-56

² DeLong DM, et al. A comparison of methods. *JAMA* 1986;256:2372-7.

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.
- Pregnant and nursing women. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). SEPTA-SIMVASTATIN should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the possible harm. If the patient becomes pregnant while taking SEPTA-SIMVASTATIN, the drug should be discontinued immediately and the patient apprised of the potential harm to the fetus. Atherosclerosis being a chronic process, discontinuation of lipid metabolism regulating drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia (see WARNINGS AND PRECAUTIONS, Pregnant Women and Nursing Women).

WARNINGS AND PRECAUTIONS

Warnings and precautions are listed in alphabetical order.

General

Before instituting therapy with SEPTA-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.

Endocrine and Metabolism

Effect on CoQ10 Levels (Ubiquinone): Significant decreases in circulating CoQ10 levels in patients treated with simvastatin and other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of CoQ10 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 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 prior to titration, 3 months after titration to the 80 mg dose, and periodically thereafter (e.g., semi-annually) 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.

SEPTA-SIMVASTATIN, as well as other HMG-CoA reductase inhibitors, 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 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.

Muscle Effects

Myopathy/Rhabdomyolysis: Effects on skeletal muscle such as myalgia, myopathy and, rarely, rhabdomyolysis have been reported in patients treated with simvastatin.

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria, have been reported with simvastatin and with other HMG-CoA reductase inhibitors.

Myopathy, defined as muscle pain or muscle weakness in conjunction with increases in creatine phosphokinase (CK) values to greater than ten times the upper limit of normal (ULN), should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or a marked elevation of CK. Patients should be advised to report promptly any unexplained muscle pain, tenderness or weakness, particularly if associated with malaise or fever. Patients who develop any signs or symptoms suggestive of myopathy should have their CK levels measured. SEPTA-SIMVASTATIN therapy should be immediately discontinued if markedly elevated CK levels are

measured or myopathy is diagnosed or suspected. 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.

Pre-disposing Factors for Myopathy/Rhabdomyolysis: SEPTA-SIMVASTATIN, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- Personal or family history of hereditary muscular disorders
- Previous history of muscle toxicity with another HMG-CoA reductase inhibitor
- Concomitant use of a fibrate or niacin (nicotinic acid)
- Uncontrolled hypothyroidism
- Alcohol abuse
- Excessive physical exercise
- Age ≥ 65 years
- Female gender
- Renal impairment
- Hepatic impairment
- Diabetes with hepatic fatty change
- Surgery and trauma
- Frailty
- Situations where an increase in plasma levels of active ingredient may occur (see DRUG INTERACTIONS)

SEPTA-SIMVASTATIN therapy should be temporarily withheld or discontinued in any patient with an acute serious condition suggestive of myopathy or predisposing to the development of rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic endocrine and electrolyte disorders, or uncontrolled seizures).

Myopathy/Rhabdomyolysis 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, Overview).

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, the HIV protease inhibitors, or the antidepressant nefazodone, particularly with higher doses of simvastatin** (see DRUG INTERACTIONS and DETAILED PHARMACOLOGY, Pharmacokinetics).

Other Drugs:

- **Gemfibrozil or other fibrates (except fenofibrate), particularly with higher doses of simvastatin** (see DRUG INTERACTIONS). When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent.
- **Cyclosporine or danazol** particularly with higher doses of simvastatin (see DRUG INTERACTIONS and DETAILED PHARMACOLOGY, Pharmacokinetics).
- **Amiodarone with higher doses of simvastatin** (see DRUG INTERACTIONS). In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone.
- **Calcium channel blockers**
 - **Verapamil with higher doses of simvastatin** (see DRUG INTERACTIONS).
 - **Diltiazem:** In a clinical trial, patients on diltiazem treated concomitantly with simvastatin 80 mg had an increased risk of myopathy. 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 diltiazem (see DRUG INTERACTIONS and DETAILED PHARMACOLOGY, Pharmacokinetics).
 - **Amlodipine:** In a clinical trial, patients on amlodipine treated concomitantly with simvastatin 80 mg had a slightly increased risk of myopathy. The risk of myopathy in patients taking simvastatin 40 mg was not increased by concomitant amlodipine (see DRUG INTERACTIONS and DETAILED PHARMACOLOGY, Pharmacokinetics).

- **Fusidic acid (oral or IV):** Patients on fusidic acid (oral or IV) treated concomitantly with simvastatin may have an increased risk of myopathy (see DRUG INTERACTIONS).
- **Niacin (≥ 1 g/day):** Myopathy, including rhabdomyolysis, has occurred in patients who were receiving co-administration of Simvastatin and other HMG-CoA reductase inhibitors with niacin, particularly in subjects with pre-existing renal insufficiency (see DRUG INTERACTIONS).

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related. In a clinical trial database in which 41,413 patients were treated with Simvastatin with 24,747 (approximately 60%) of whom were enrolled in studies with a median follow-up of at least 4 years, the incidence of myopathy was approximately 0.03%, 0.08% and 0.61% at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

In a clinical trial in which patients with a history of myocardial infarction were treated with Simvastatin 80 mg/day (mean follow-up 6.7 years), the incidence of myopathy was approximately 1.0% compared with 0.02% for patients on 20 mg/day. Approximately half of these myopathy cases occurred during the first year of treatment. The incidence of myopathy during each subsequent year of treatment was approximately 0.1%.

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 any unexplained muscle pain, tenderness or weakness. Simvastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. The presence of these symptoms, and a CK level >10 times the upper limit of normal indicates myopathy. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved. Periodic CK determinations may be considered in patients starting therapy with simvastatin or whose dose is being increased. Periodic CK determinations are recommended for patients titrating to the 80-mg dose. 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, clarithromycin or telithromycin 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, danazol, gemfibrozil, or other fibrates (except fenofibrate). The combined use of simvastatin with gemfibrozil should be avoided unless the benefits are likely to outweigh the increased risks of this drug combination. The benefits of the use of simvastatin in patients receiving other fibrates (except fenofibrate), cyclosporine, or danazol should be carefully weighed against the risks of these drug combinations. Caution should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone. Addition of fibrates 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 with 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.

The dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with diltiazem, unless the clinical benefit is likely to outweigh the increased risk of myopathy.

Caution should be used when prescribing amlodipine with simvastatin 80 mg as there is a slight increase in the risk of myopathy with concomitant use.

The dose of simvastatin should not exceed 40 mg daily in Chinese patients receiving concomitant medication with niacin (≥ 1 g/day). Interim safety data of an ongoing, double blind, randomised cardiovascular outcome study has shown that the incidence of myopathy was higher in Chinese patients versus non-Chinese patients.

Patients on fusidic acid (oral or IV) and simvastatin should be closely monitored for

symptoms and/or signs of myopathy. Temporary suspension of simvastatin treatment may be considered.

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 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, SEPTA-SIMVASTATIN should be discontinued.

Special Populations

Pregnant Women: 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, simvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with 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 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 SEPTA-SIMVASTATIN should not nurse (see CONTRAINDICATIONS).

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 overall frequency and severity of clinical or laboratory adverse findings. However, in a clinical trial of patients treated with simvastatin 80 mg/day, patients ≥ 65 years of age had an increased risk of myopathy compared to patients <65 years of age.

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

Elderly patients may be more susceptible to myopathy (see WARNINGS AND PRECAUTIONS, Muscle Effects – Pre-disposing Factors for Myopathy/Rhabdomyolysis).

Monitoring and Laboratory Tests

In the differential diagnosis of chest pain in a patient on therapy with SEPTA-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 $\geq 0.5\%$ 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 and CLINICAL TRIALS) 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.

Ophthalmologic: See WARNINGS AND PRECAUTIONS, Ophthalmologic.

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 (CK) levels three or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CK. 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 post-marketing experience with simvastatin, regardless of causality assessment.

Gastrointestinal:

Vomiting

Hematologic:

Anemia

Leukopenia

Purpura

Hepatic/Pancreatic:

Hepatitis

Hepatic failure with fatal or liver transplant outcome have been reported.

Jaundice

Pancreatitis

Laboratory Tests:

Elevated alkaline phosphatase and γ -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 BIBLIOGRAPHY)

Memory impairment

Pulmonary:

Interstitial lung disease

Psychiatric:

Depression

Insomnia

Reproductive system and breast disorders:

Erectile dysfunction

Sensitivity:

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

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, hypospermia, gynecomastia, psychic disturbances including anxiety, sleep disturbances including nightmares.

DRUG INTERACTIONS**Overview: CYP3A4 Interactions**

Simvastatin itself is a substrate for CYP3A4. However, 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). 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

• **Interactions with Lipid-Lowering Drugs That Can Cause Myopathy When Given Alone**

The risk of myopathy may also be increased by the following lipid-lowering drugs that are not potent inhibitors of CYP3A4, but which can cause myopathy when given alone (see below and WARNINGS AND PRECAUTIONS).

- **Gemfibrozil**

The risk of myopathy/rhabdomyolysis is increased by gemfibrozil (see DOSAGE AND ADMINISTRATION).

- **Other Fibrates (except fenofibrate)**

These drugs (except fenofibrate) 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). When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent.

• **Concomitant Therapy with other Lipid Metabolism Regulators**

- **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.

• **Other drugs:**

- **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.
- **Cyclosporine or Danazol:** The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine or danazol particularly with higher doses of simvastatin (see WARNINGS AND PRECAUTIONS, Myopathy/Rhabdomyolysis Caused by Drug Interactions).
 - **-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.
 - **-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.
 - **Calcium channel blockers:**
 - **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%).
 - **Diltiazem:** The risk of myopathy/rhabdomyolysis is increased by concomitant administration of diltiazem with simvastatin 80 mg. 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 diltiazem (see WARNINGS AND PRECAUTIONS, Myopathy/Rhabdomyolysis Caused by Drug Interactions).
 - **Amlodipine:** Patients on amlodipine treated concomitantly with simvastatin 80 mg have a slightly increased risk of myopathy (see WARNINGS AND PRECAUTIONS, Myopathy/Rhabdomyolysis Caused by Drug Interactions).
 - **Niacin (nicotinic acid) (≥1 g/day):** Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥1 g/day) of niacin (see WARNINGS AND PRECAUTIONS, Myopathy/Rhabdomyolysis Caused by Drug Interactions).

- **Fusidic Acid (oral or IV):** Patients on fusidic acid (oral or IV) treated concomitantly with simvastatin may have an increased risk of myopathy/rhabdomyolysis (see WARNINGS AND PRECAUTIONS, Myopathy/Rhabdomyolysis Caused by Drug Interactions).
- **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

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Patients should be placed on a standard cholesterol-lowering diet before receiving SEPTA-SIMVASTATIN, and should continue on this diet during treatment with SEPTA-SIMVASTATIN. If appropriate, a program of weight control and physical exercise should be implemented.
- Prior to initiating therapy with SEPTA-SIMVASTATIN, secondary causes for elevations in plasma lipid levels should be excluded. A lipid profile should also be performed.
- **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 SEPTA-SIMVASTATIN is 40 mg/day

given as a single dose in the evening. Drug therapy can be initiated simultaneously with diet and exercise.

- **Patients with Hyperlipidemia (who are not in the risk categories above):** The usual starting dose is 10 mg/day given as a single dose in the evening. Patients who require a large reduction 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 SEPTA-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 SEPTA-SIMVASTATIN if cholesterol levels fall below the desired range.**
- **Concomitant Therapy with other Lipid Metabolism Regulators.** If SEPTA-SIMVASTATIN is used with gemfibrozil, the dose of SEPTA-SIMVASTATIN should not exceed 10 mg/day (See DRUG INTERACTIONS, Concomitant Therapy with other Lipid Metabolism Regulators).
- In patients taking cyclosporine, danazol, therapy should begin at 5 mg/day and not exceed 10 mg/day.
- In patients taking amiodarone or verapamil concomitantly with SEPTA-SIMVASTATIN, the dose of SEPTA-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).
- In patients taking diltiazem concomitantly with SEPTA-SIMVASTATIN, the dose of SEPTA-SIMVASTATIN should not exceed 40 mg/day (see WARNINGS AND PRECAUTIONS, Measures to reduce the risk of myopathy/rhabdomyolysis caused by drug interactions and DRUG INTERACTIONS).
- The dosage of SEPTA-SIMVASTATIN should be individualized according to baseline LDL-C, total-C/HDL-C ratio and/or TG levels to achieve the recommended desired lipid values at the lowest possible dose and the patient response. Lipid levels should be monitored periodically and, if necessary, the dose of SEPTA-SIMVASTATIN adjusted based on desired lipid levels.

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 should be used only for those patients who have not achieved their LDL-C goal utilizing the 40-mg dose (see WARNINGS AND PRECAUTIONS, Myopathy/Rhabdomyolysis). 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.

Dosage in Renal Insufficiency

Because simvastatin does not undergo significant renal excretion, modification of dosage should not be necessary in patients with mild to moderate renal insufficiency. However, caution should be exercised when simvastatin is administered to patients with severe renal insufficiency; such patients should be started at 5mg/day and be closely monitored (see WARNINGS AND PRECAUTIONS, Muscle Effects and Renal).

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 the next dose: only the prescribed dose should be taken at the appointed time. **A double dose should not be taken.**

OVERDOSAGE

For the management of a suspected drug overdose, contact your regional Poison Control Centre.

A few cases of overdose have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae. General measures should be adopted.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

SEPTA-SIMVASTATIN is a lipid-lowering agent derived synthetically from a fermentation product of *Aspergillus terreus*.

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

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Simvastatin Tablets as 5mg, 10mg, 20mg, 40mg and 80mg strengths.

SEPTA-SIMVASTATIN tablets, 5 mg is buff colored, shield shaped, biconvex, film-coated tablets, engraved with '5' on one face and engraved with 'S' on the other. Dispensed in Blisters of 30's (3x10's) and HDPE bottles of 100's, 250's and 500's.

SEPTA-SIMVASTATIN tablets, 10 mg is peach colored, shield shaped, biconvex, film-coated tablets, engraved with '10' on one face and engraved with 'S' on the other. Dispensed in Blisters of 30's (3x10's) and HDPE bottles of 100's, 250's and 500's.

SEPTA-SIMVASTATIN tablets, 20 mg is tan colored, shield shaped, biconvex, film-coated tablets, engraved with '20' on one face and engraved with 'S' on the other. Dispensed in Blisters of 30's (3x10's) and HDPE bottles of 100's, 250's and 500's.

SEPTA-SIMVASTATIN tablets, 40 mg is brick red colored, shield shaped, biconvex, film-coated tablets, engraved with '40' on one face and engraved with 'S' on the other. Dispensed in Blisters of 30's (3x10's) and HDPE bottles of 100's, 250's and 500's.

SEPTA-SIMVASTATIN tablets, 80 mg is brick red colored, caplet shaped, biconvex, film-coated tablets, engraved with '80' on one face and engraved with 'S' on the other. Dispensed in Blisters of 30's (3x10's) and HDPE bottles of 100's, 250's and 500's.

Non-medicinal ingredients: Ascorbic acid, butylated hydroxyanisole, citric acid monohydrate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, talc, and titanium dioxide. Tablets 5 mg, 10 mg and 20 mg, 40mg and 80mg contain yellow ferric oxide. Tablets 10 mg, 20 mg, 40 mg and 80 mg also contain red ferric oxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

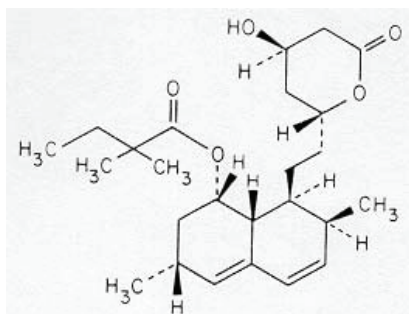
Proper name: Simvastatin

Chemical name: [1S-[1 α ,3 α ,7 β ,8 β (2S*,4S*), 8 α]]-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.

Molecular Formula: C₂₅H₃₈O₅

Molecular Mass: 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, K_p (where K_p = 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

COMPARATIVE BIOAVAILABILITY

A blinded, randomized, open label, balanced, two treatment, two period, two sequence, single dose, two way crossover, pivotal bioequivalence study of SEPTA-SIMVASTATIN 80mg tablets of Septa Pharmaceuticals Inc., and Zocor® (containing Simvastatin 80mg) tablets of Merck Frosst Canada Ltd., Canada in 79 healthy, adult, human male and female subjects under fasting conditions.

Simvastatin Tablets (1 x 80 mg tablet)				
From measured data uncorrected for potency Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90 % Confidence Interval#
AUC _T [‡] (ng*hr/mL)	196.45 227.98 (51.68)	183.62 217.01 (60.52)	106.99	99.63 – 114.89
AUC _I (ng*hr/mL)	213.17 243.85 (48.86)	197.79 232.81 (59.42)	107.78	100.20 – 115.94
C _{max} (ng/mL)	48.39 59.28 (64.68)	49.82 59.00 (60.13)	97.11	88.07 – 107.09
T _{max} [§] (h)	1.85 (54.11)	1.75 (62.13)		
T _{1/2} [§] (h)	5.36 (46.35)	5.26 (48.25)		

* SEPTA-SIMVASTATIN tablets 80mg manufactured by Septa Pharmaceuticals Inc.,

† Zocor 80mg tablets (manufactured by Merck Frosst Canada Ltd), purchased in Canada.

§ Expressed as the arithmetic mean (CV%) only

Based on the least square mean estimate

Clinical Trials in Adult Patients

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 and Combined (Mixed) Hyperlipidemia (Mean Percent Change from Baseline after 6 to 24 Weeks)

TREATMENT	N	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	TG (median)
<u>Lower Dose Comparative Study</u>					
Simvastatin- 5 mg*	109	-19	-26	10	-12
Simvastatin- 10 mg*	110	-23	-30	12	-15
<u>Scandinavian Simvastatin Survival Study</u>					

TREATMENT	N	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	TG (median)
Placebo	2223	-1	-1	0	-2
Simvastatin- 20 mg*	2221	-28	-38	8	-19
<u>Upper Dose Comparative Study</u>					
Simvastatin - 40 mg*	433	-31	-41	9	-18
Simvastatin - 80 mg*	664	-36	-47	8	-24
<u>Multicenter Combined Hyperlipidemia Study</u>					
Placebo	125	1	2	3	-4
Simvastatin - 40 mg*	123	-25	-29	13	-28
Simvastatin - 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 ≤ 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 Fredrickson 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 comparing placebo or Simvastatin 20, 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 = 7.23 (279) and 6.04 mmol/L (233 mg/dL); LDL-C = 3.11 (120) and 2.59 (100); HDL-C = 0.96 (37) and 0.91 (35); TG = 4.93 (435) and 5.01 (441)); VLDL-C = 2.56 (99) and 2.44 (94); non-HDL-C = 6.29 (243) and 5.13 (198).

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 a 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 CHOLESTEROL CHANGE, %		LDL-CHOLESTEROL CHANGE, %	
	Simvastatin 20mg	Simvastatin 40mg	Simvastatin 20mg	Simvastatin 40mg
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 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 (median)	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 40mg 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 6. 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 (median)	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

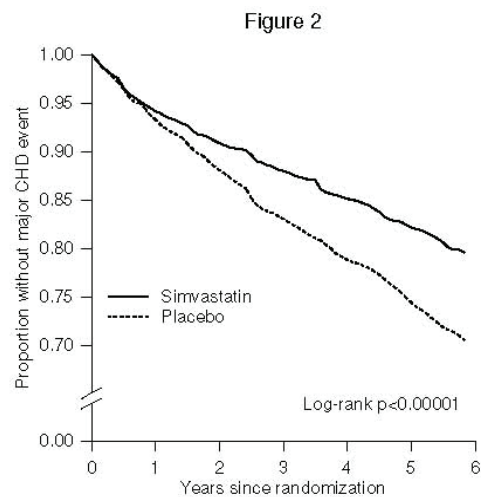
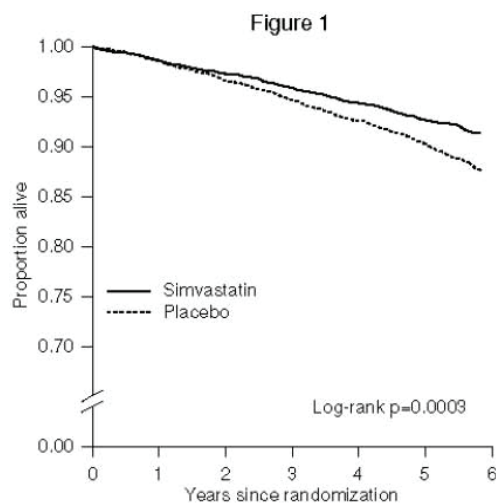
[†] (Stratum I, baseline LDL < 195 mg/dL)

^{††} (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 (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).



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.

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 40 mg 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 of non-fatal 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., patients allocated placebo took a statin, or patients allocated simvastatin did not take the study drug).

Table 7. Summary of Results of HPS

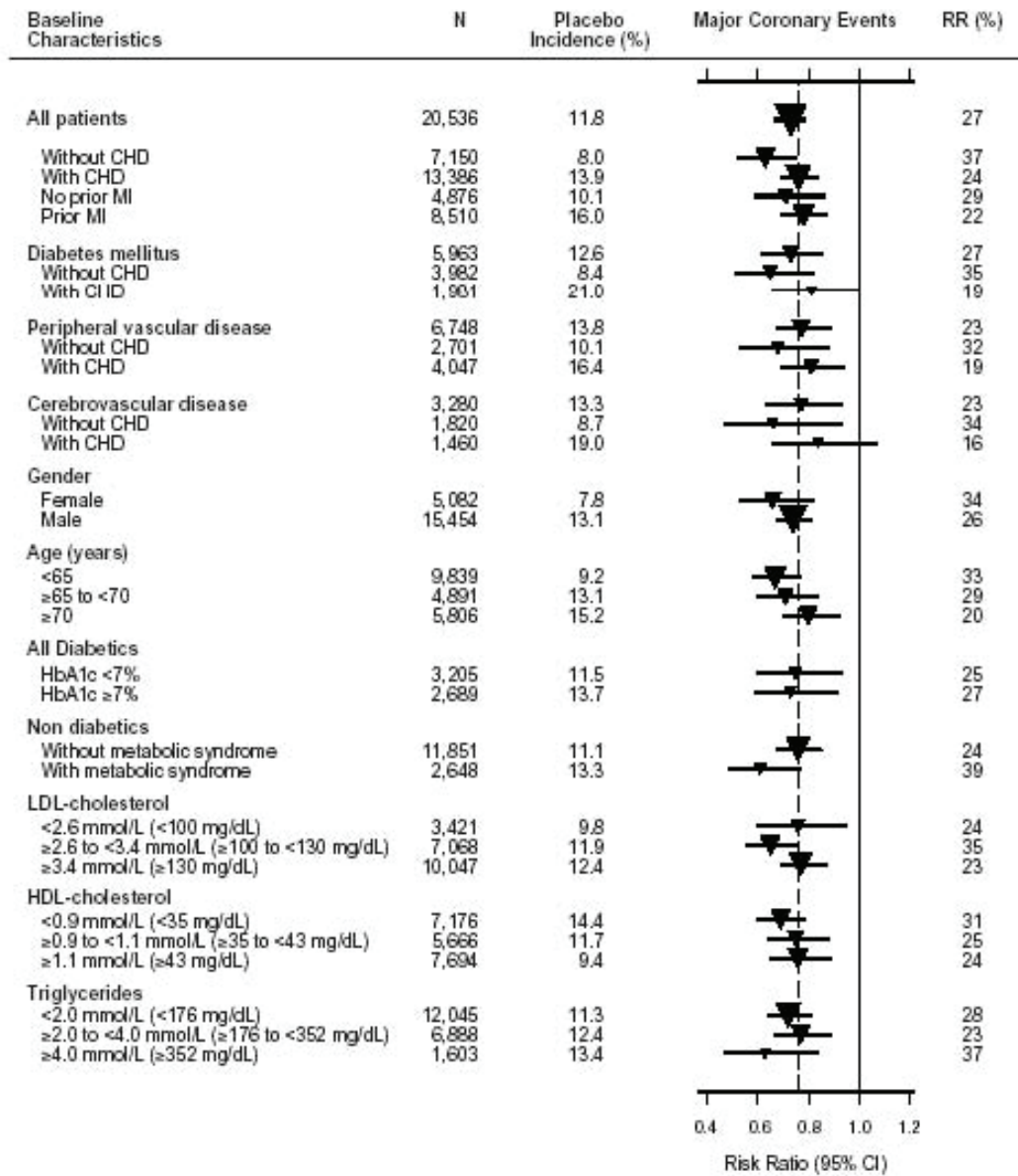
Endpoint	Simvastatin (n=10,269) (%)	Placebo (n=10,267) (%)	Absolute Risk Reduction*(%) (95% CI)	Relative Risk Reduction (%) (95% CI)	P value
Primary					
Mortality	12.9	14.6	1.7 (0.8-2.7)	13 (6-19)	P=0.0003
CHD Mortality	5.7	6.8	1.2 (0.5-1.8)	18 (8-26)	P=0.0005
Secondary					
Major coronary events ****	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 event rates ** See Figure 3 (results by baseline characteristics)

*** A composite of non-fatal myocardial infarction or CHD deaths

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

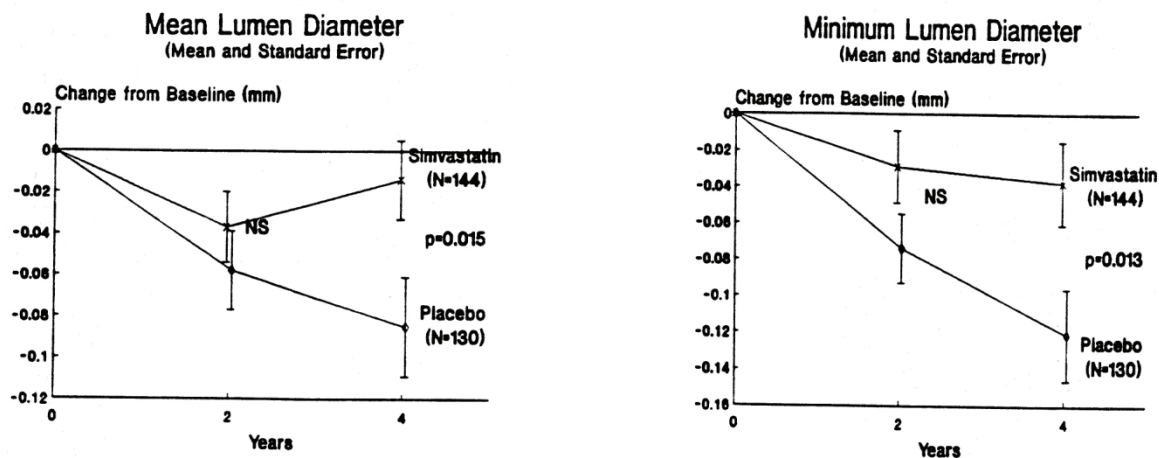
Figure 3 -The Beneficial Effects of Treatment with simvastatin on Major Coronary Events in Heart Protection Study



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 point 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 the 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 hypercholesterolemia (FH). It is not clear to what extent these findings can be extrapolated to the familial hypercholesterolemic subpopulation not studied.

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 β -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 β -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.

Although the mechanism is not fully understood, cyclosporine has been shown to increase the AUC of HMG-CoA reductase inhibitors. The increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4.

In a pharmacokinetic study, concomitant administration of diltiazem caused a 2.7-fold increase in exposure of simvastatin acid, presumably due to inhibition of CYP3A4.

In a pharmacokinetic study, concomitant administration of amlodipine caused a 1.6-fold increase in exposure of simvastatin acid.

In a pharmacokinetic study, the coadministration of a single dose of niacin extended-release 2 g with simvastatin 20 mg resulted in a modest increase in the AUC of simvastatin and simvastatin

acid (1.4- and 1.6-fold, respectively) and in the C_{max} of simvastatin acid (1.8-fold) plasma concentrations.

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 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 IC₅₀ values for inhibition of sterol synthesis in cultured animal cells by simvastatin, and determined by measuring the incorporation of ¹⁴C-acetate into ¹⁴C-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 ¹⁴C-acetate into ¹⁴C-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 ID₅₀ 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 β -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	LD₅₀ 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	-	NA	-	+	-
Eye (lens)	+	+	-	-	-
Stomach (non-glandular)	NA	+	+	NA	NA
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 transaminases	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 man). 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 to 100 mg/kg/day (31 to 63 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 (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/m² body surface area) has been shown to reduce the fetal plasma levels of mevalonate.

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PART III: CONSUMER INFORMATION

PrSEPTA-SIMVASTATIN Simvastatin Tablets, USP

This leaflet is part III of a three-part "Product Monograph" published when SEPTA-SIMVASTATIN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SEPTA-SIMVASTATIN. Contact your physician or pharmacist if you have any questions about the drug.

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.**

ABOUT THIS MEDICATION

SEPTA-SIMVASTATIN is the brand name for the substance - simvastatin, available **only on prescription** from your physician.

What the medication is used for:

Your physician has prescribed SEPTA-SIMVASTATIN to lower the levels of cholesterol and fatty substances called triglycerides in your blood and to reduce the health risks associated with Coronary Heart Disease (CHD).

Elevated cholesterol can cause CHD by clogging the blood vessels (atherosclerosis) that carry oxygen and nutrients to the heart.

If you have CHD or other signs of atherosclerosis such as previous stroke, symptoms of peripheral vascular disease, or diabetes (regardless of the amount of cholesterol in your blood), SEPTA-SIMVASTATIN should lessen the risk of heart attack or stroke.

You can also benefit from taking SEPTA-SIMVASTATIN if you have high levels of cholesterol with or without associated high triglycerides (primary hypercholesterolemia, or combined hyperlipidemia) and homozygous familial

hypercholesterolemia (high cholesterol inherited from both parents).

As part of your treatment plan to lower cholesterol, and depending on your health and lifestyle, your physician may recommend a diet to reduce cholesterol and other measures such as exercise and weight control.

What it does:

Simvastatin is one of the 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. 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 cholesterol (LDL-C)] and fatty substances called triglycerides in your blood.

SEPTA-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.

When it should not be used:

Do not take SEPTA-SIMVASTATIN if you are:

- allergic to any of its components
- diagnosed with active liver disease
- pregnant or breast-feeding

What the medicinal ingredient is:

Simvastatin

What the nonmedicinal ingredients are:

Ascorbic acid, butylated hydroxyanisole, citric acid monohydrate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, talc, and titanium dioxide.

Tablets 5 mg, 10 mg, 20 mg, 40mg and 80mg contain yellow ferric oxide. Tablets 10 mg, 20 mg, 40 mg and 80 mg also contain red ferric oxide.

What dosage forms it comes in:

Tablet 5 mg (buff), 10 mg (peach), 20 mg (tan), 40 mg (brick red) and 80 mg (brick red)

WARNINGS AND PRECAUTIONS

Before taking SEPTA-SIMVASTATIN, tell your physician or pharmacist if you:

- are pregnant, intend to become pregnant, are breast-feeding or intend to breast-feed
- have thyroid problems
- regularly drink *three or more* alcoholic drinks daily
- are taking any other cholesterol lowering medication such as fibrates (gemfibrozil, fenofibrate), niacin or ezetimibe
- are taking any other medications, including prescription, nonprescription and natural health products as drug interactions are possible
- have a family history of muscular disorders
- had any past problems with the muscles (pain, tenderness), after using an HMG-CoA reductase inhibitor (“statin”) such as atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (MEVACOR[®]), pravastatin (Pravachol) or rosuvastatin (Crestor), or have developed an allergy or intolerance to them
- have kidney or liver problems
- have diabetes
- have undergone surgery or other tissue injury
- do excessive physical exercise
- are of childbearing age. Cholesterol compounds are essential elements for the development of a fetus. Cholesterol-lowering drugs can harm the fetus. If you are of childbearing age, discuss with your physician the potential hazards to the fetus and the importance of birth control methods.
- become pregnant. SEPTA-SIMVASTATIN should not be used by pregnant women. If you become pregnant, discontinue use immediately and discuss with your physician.

INTERACTIONS WITH THIS MEDICATION

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

Because taking SEPTA-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)
- danazol
- antifungal agents (such as itraconazole or ketoconazole)
- fibrates/fibric acid derivatives (bezafibrate and gemfibrozil) (drug to treat lipids problems)
- the antibiotics (erythromycin, clarithromycin, telithromycin, and fusidic acid [oral or intravenous])
- 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 or amlodipine (drugs used to treat high blood pressure, angina, or other heart conditions)

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

Also tell your doctor if you are taking niacin or a niacin-containing product and are Chinese.

PROPER USE OF THIS MEDICATION

Usual Dose:

- Take your medication exactly as your physician instructed. Do not change the

- dose unless directed by a physician. It is usually recommended as a single dose with the evening meal. For adults, your physician may adjust your dose to a maximum of 80 mg a day, given as a single dose in the evening. The 80-mg dose is only for patients who have not reached their cholesterol goal on the 40-mg dose. It is important to continue taking the tablets as instructed. **Do not alter the dosage or stop taking the medicine without consulting your physician.**
- Carefully follow any measures that your physician has recommended for diet, exercise or weight control.
- When taking SEPTA-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.
- When taking SEPTA-SIMVASTATIN concurrently with cholestyramine or any other resin, an interval of at least two hours should be maintained between the two drugs.
- 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.

Overdose:

Contact your physician immediately.

In case of drug overdosage, contact a health care practitioner, hospital emergency department or original Poison Control Center immediately, even if there are no symptoms.

Missed Dose:

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.**

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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:**

- Fever
- Blurred vision
- Muscle effects
- Liver problems (sometimes serious) (See SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM.)

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
- Memory loss
- Trouble sleeping
- Depression
- Erectile dysfunction
- Breathing problems including persistent cough and/or shortness of breath or fever

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptoms / effects		Talk with your physician or pharmacist		Stop taking drug and call your physician or pharmacist
		Only if severe	In all cases	
Rare	Allergic reactions			√
	Brownish or discoloured urine		√	
	Symptoms of liver problems (abdominal pain, dark urine, itchy skin, nausea or vomiting, pale stools, yellowing of skin or eyes)		√	
	Generalized weakness, especially if you do not feel well		√	
	Unexplained muscle pain		√	
	Muscle tenderness or muscle weakness		√	

Side effects such as myalgia (muscle pain), myopathy (muscle disease with aching or weakness), rhabdomyolysis (a muscle wasting disease), associated tenderness, and rare cases of rhabdomyolysis leading to kidney failure have been reported with other drugs of this class, known as HMG-CoA reductase inhibitors (“statins”), including simvastatin. This risk of muscle breakdown is greater for patients taking higher doses of simvastatin. This risk of muscle breakdown is greater for older patient (65 years of age and older), female patients, patients with abnormal kidney function and patients with thyroid problems.

As these muscle problems are on rare occasions serious, you should contact your physician promptly if you experience any of the following:

- muscle pain that you cannot explain
- muscle tenderness or muscle weakness
- generalized weakness, especially if you do not feel well (i.e., fever or fatigue)
- brownish or discoloured urine

This is not a complete list of side effects. For any unexpected effects while taking SEPTA-SIMVASTATIN, contact your physician or pharmacist.

HOW TO STORE IT

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

Keep all medicines out of the reach of children.

Do not use outdated medicine.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to:
 - Canada Vigilance Program
 - Health Canada
 - Postal Locator 0701E
 - Ottawa, Ontario, K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

Or at Septa Pharmaceuticals Inc., by one of the following 2 ways:

- Call at **(905) 670-0098 Ext 231** or
- Complete a Canada Vigilance Reporting Form and:
 - Fax to **(905) 670-0133**

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program or Merck do not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals by Septa Pharmaceuticals Inc.

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