PRODUCT MONOGRAPH

PrMYLAN-SIMVASTATIN

(Simvastatin Tablets)

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

USP

Lipid Metabolism Regulator

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Canada
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablet / 5 mg, 10 mg, 20 mg, 40 mg & 80 mg	Ascorbic acid, butylated hydroxyanisole, citric acid, dehydrated alcohol, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, talc and titanium dioxide. Tablets 5 mg also contain polydextrose. Tablets 5, 10, 40 and 80 mg contain triacetin. Tablets 5 and 20 mg contain polyethylene glycol. Tablets 5, 10, 20, 40 and 80 mg contain red iron oxide. Tablets 5, 10 and 20 mg contain yellow iron oxide. Tablets 20 mg contain black iron 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, MYLAN-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, simvastatin slows the progression of coronary atherosclerosis, including reducing the development of new lesions and new total occlusions.

Hyperlipidemia

MYLAN-SIMVASTATIN is indicated as an adjunct to diet, at least equivalent to the American Heart Association (AHA) Step 1 diet, for the reduction of elevated total cholesterol (total-C) and Low-Density Lipoprotein-cholesterol (LDL-C), apolipoprotein B (apo B), and triglycerides (TG) levels in patients with primary hypercholesterolemia (Type IIa)* or combined (mixed) hyperlipidemia (Type IIb)* when the response to diet and other nonpharmacological measures alone has been inadequate. MYLAN-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 (HoFH). 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 MYLAN-SIMVASTATIN is being considered have an elevated LDL-C level as the cause for an elevated total serum cholesterol. This may be particularly relevant for patients with total triglycerides over 4.52 mmol/L (400 mg/dL) or with markedly elevated HDL-C values, where non-LDL fractions may contribute significantly to total cholesterol levels without apparent increase in cardiovascular risk. In most patients LDL-C may be estimated according to the following equation:

LDL-C (mmol/L) = Total cholesterol - [(0.37 x triglycerides) + HDL-C]**
LDL-C (mg/dL) = Total cholesterol - [(0.16 x triglycerides) + HDL-C]

When total triglycerides are greater than 4.52 mmol/L (400 mg/dL) this equation is less accurate. In such patients, LDL-C may be obtained by ultracentrifugation.

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

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

Pediatric Patients with Heterozygous Familial Hypercholesterolemia

MYLAN-SIMVASTATIN is indicated as an adjunct to diet to reduce total-C, LDL-C, TG, and Apo B levels in adolescent boys and girls who are at least one year post-menarche, 10-17 years of age, with heterozygous familial hypercholesterolemia (HeFH).

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). MYLAN-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 MYLAN-SIMVASTATIN, the drug should be discontinued immediately and the patient appraised 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).
- Concomitant administration of potent CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone and drugs containing cobicistat) (see WARNINGS AND PRECAUTIONS, Muscle Effects and DRUG INTERACTIONS).
- Concomitant administration of gemfibrozil, cyclosporine, or danazol (see WARNINGS AND PRECAUTIONS, Muscle Effects and DRUG INTERACTIONS.

WARNINGS AND PRECAUTIONS

Warnings and precautions are listed in alphabetical order.

General

Before instituting therapy with MYLAN-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 doctors of the prior use of MYLAN-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.

Due to the increased risk of myopathy/rhabdomyolysis, particularly during the first year of treatment, 80 mg/day of MYLAN-SIMVASTATIN is discouraged (see Muscle Effects). Consider alternative treatment strategies (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

Endocrine and Metabolism

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

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

Endocrine and Metabolism: 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., spironolactone, or cimetidine) that may decrease the levels of endogenous steroid hormones (see DRUG INTERACTIONS).

Increases in fasting glucose and HbA1c levels have been reported with inhibitors of HMG-CoA reductase as a class. For some patients, at high risk of diabetes mellitus, hyperglycemia was sufficient to shift them to the diabetes status. The benefit of treatment continues to outweigh the small increased risk. Periodic monitoring of these patients is recommended.

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 80 mg should receive an additional test prior to titration, 3 months after titration to 80 mg, 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. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy (see WARNINGS AND PRECAUTIONS, Muscle Effects).

There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking simvastatin, regardless of the dose. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with MYLAN-SIMVASTATIN, promptly interrupt therapy. If an alternate etiology is not found, do not restart MYLAN-SIMVASTATIN.

MYLAN-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 MYLAN-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. **Therefore, 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, particularly if associated with malaise or fever.** Periodic CK determinations may be considered in patients starting therapy with simvastatin or whose dose is being increased. Patients who develop any signs or symptoms suggestive of myopathy should have their CK levels measured. **MYLAN-SIMVASTATIN therapy should be immediately discontinued if markedly elevated CK levels are measured or myopathy is diagnosed or suspected.** In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved (see ADVERSE REACTIONS). Periodic CK determinations are recommended for patients titrating to 80 mg. There is no assurance that such monitoring will prevent myopathy. 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 (i.e., elevated simvastatin and simvastatin acid plasma levels), which may be due, in part, to interacting drugs that interfere with simvastatin metabolism and/or transporter pathways (see DRUG INTERACTIONS).

Pre-disposing Factors for Myopathy/Rhabdomyolysis: MYLAN-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)

MYLAN-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).

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 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 12,064 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 risk of myopathy/rhabdomyolysis is greater in patients taking 80 mg of simvastatin daily compared with other statin-based therapies with similar LDL-C-lowering efficacy. Therefore, 80 mg/day of MYLAN-SIMVASTATIN is discouraged (see DOSAGE AND ADMINISTRATION). The 80 mg dosage should be restricted to patients who have been taking this dose chronically with no evidence of muscle toxicity or to patients at high risk for cardiovascular complications who do not tolerate other statins and in whom the benefits are expected to outweigh the potential risks.

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.

In a clinical trial in which patients at high risk of cardiovascular disease were treated with simvastatin 40 mg/day (median follow-up 3.9 years), the incidence of myopathy was approximately 0.05% for non-Chinese patients (n=7367) compared with 0.24% for Chinese patients (n=5468). While the only Asian population assessed in this clinical trial was Chinese, caution should be used when prescribing simvastatin to Asian patients and the lowest dose necessary should be employed.

The risk of myopathy and rhabdomyolysis during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of drugs that interfere with their metabolism via the cytochrome P-450 isoform 3A4 (see DRUG INTERACTIONS).

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

Contraindicated Drugs

Potent inhibitors of CYP3A4: for example, the antifungal azoles (itraconazole, ketoconazole, posaconazole and voriconazole), the antibiotics (erythromycin, clarithromycin and telithromycin), the HIV protease inhibitors, HCV protease inhibitors (boceprevir, telaprevir), the antidepressant nefazodone (not marketed in Canada), or drugs containing cobicistat. If short-term treatment with potent CYP3A4 inhibitors is unavoidable, therapy with simvastatin should be suspended during the course of treatment (see CONTRAINDICATIONS, DRUG INTERACTIONS and DETAILED PHARMACOLOGY, Pharmacokinetics).

Gemfibrozil, cyclosporine or danazol: Concomitant use of these drugs with simvastatin is contraindicated (see CONTRAINDICATIONS, DRUG INTERACTIONS and DETAILED PHARMACOLOGY, Pharmacokinetics).

Other Drugs: fibrates other than gemfibrozil (see CONTRAINDICATIONS) or fenofibrate, amiodarone, calcium channels blockers (verapamil, diltiazem and amlodipine), fusidic acid[1], niacin, lomitapide and grazoprevir/elbasvir (see DRUG INTERACTIONS, Other drug interactions).

Daptomycin: Both daptomycin and HMG-CoA reductase inhibitors are independently associated with skeletal muscle effects. Reports of myopathy and/or rhabdomyolysis have been observed with simvastatin coadministered with daptomycin therefore, MYLAN-SIMVASTATIN should be temporarily suspended in patients taking daptomycin particularly those with pre-disposing factors for myopathy/rhabdomyolysis (see DRUG INTERACTIONS, Other drug interactions).

Immune-Mediated Necrotizing Myopathy

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy associated with statin use. IMNM is characterized by:

- Proximal muscle weakness and elevated creatine kinase, which persist despite discontinuation of statin treatment
- Muscle biopsy showing necrotizing myopathy without significant inflammation
- Improvement with immunosuppressive agents

Ophthalmologic

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

Renal

MYLAN-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, Muscle Effects).

Higher dosages 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, Muscle Effects and DRUG INTERACTIONS).**

Skin

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

Special Populations

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

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

Pediatrics: Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least one year post-menarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses greater than 40 mg have not been studied in this population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls (see DOSAGE AND ADMINISTRATION; ADVERSE REACTIONS; ACTION AND CLINICAL PHARMACOLOGY). Adolescent females should be counseled on appropriate contraceptive methods while on simvastatin therapy (see CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women). Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

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 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, Muscle Effects 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 MYLAN-SIMVASTATIN cardiac and noncardiac fractions of serum transaminase and creatine phosphokinase levels should be determined.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

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

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

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

In the Scandinavian Simvastatin Survival Study (4S) (see DETAILED PHARMACOLOGY 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. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy (see WARNINGS AND PRECAUTIONS, Muscle Effects).

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, Muscle Effects 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.

Endocrine disorders:
Increases in fasting glucose and HbA1c levels have been reported with simvastatin. Diabetes mellitus has been reported with statins, including simvastatin.

Gastrointestinal:
Vomiting

Hematologic:
Anemia
Leukopenia
Purpura

Hepatic/Pancreatic:
Hepatitis
Fatal and non-fatal hepatic failure with liver transplant outcome have been reported, regardless of the dose.
Jaundice
Pancreatitis

Laboratory Tests:
Elevated alkaline phosphatase and γ-glutamyl transpeptidase
Increased HbA1c and fasting serum glucose levels.

Muscular:
Rhabdomyolysis

Muscle Cramps
Myalgia
There have been rare reports of immune-mediated necrotizing myopathy with statins (see **WARNINGS AND PRECAUTIONS - Muscle Effects**).

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

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with simvastatin use, regardless of the dose. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

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:

- Anaphylaxis
- 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.

Pediatric Patients (ages 10-17 years)
In a study involving pediatric patients 10-17 years of age with heterozygous familial hypercholesterolemia (n = 175), the safety and tolerability profile of the group treated with simvastatin was generally similar to that of the group treated with placebo (see WARNINGS AND PRECAUTIONS, Pediatrics; ACTION AND CLINICAL PHARMACOLOGY).

DRUG INTERACTIONS

Multiple mechanisms may contribute to potential interactions with HMG Co-A reductase inhibitors. Drugs or herbal products that inhibit certain enzymes (e.g. CYP3A4) and/or transporter (e.g. OATP1B) pathways may increase simvastatin and simvastatin acid plasma concentrations and may lead to an increased risk of myopathy/rhabdomyolysis.

Consult the prescribing information of all concomitantly used drugs to obtain further information about their potential interactions with simvastatin and/or the potential for enzyme or transporter alterations and possible adjustments to dose and regimens.

Contraindicated drugs
Concomitant use of the following drugs is contraindicated:

Potent inhibitors of CYP3A4: 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. Concomitant use of drugs labeled as having a potent inhibitory effect on CYP3A4 (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone, drugs containing cobicistat) is contraindicated (see CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS, Muscle Effects, DETAILED PHARMACOLOGY, Pharmacokinetics).

Gemfibrozil, Cyclosporine or Danazol: Concomitant use of these drugs with simvastatin is contraindicated (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Muscle Effects, DETAILED PHARMACOLOGY, Pharmacokinetics).

Other drug interactions

Fusidic Acid (oral or IV): Fusidic acid must not be co-administered with statins. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. Patients on fusidic acid (oral or IV) treated concomitantly with simvastatin have an increased risk of myopathy/rhabdomyolysis (see DETAILED PHARMACOLOGY, Pharmacokinetics). In patients where the use of systemic fusidic acid is considered essential, simvastatin should be discontinued throughout the duration of fusidic acid treatment. In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g. for the treatment of severe infections, the doctor decision and justification for the co-administration of simvastatin and fusidic acid is required, on a case-by-case basis under close medical supervision, and after assessment of the risk involved to the patient.

Other Fibrates: The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with fibrates other than gemfibrozil (see CONTRAINDICATIONS) or fenofibrate; these lipid-lowering drugs can cause myopathy when given alone. 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. 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.

Amiodarone: In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone. **The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone** (see DOSAGE AND ADMINISTRATION).

Calcium Channel Blockers:

- **Verapamil or diltiazem:** In a clinical trial, patients on diltiazem treated concomitantly with simvastatin 80 mg had an increased risk of myopathy. **The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with verapamil or diltiazem.**

- **Amlodipine:** In a clinical trial, patients on amlodipine treated concomitantly with simvastatin 80 mg had a slightly increased risk of myopathy. **The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amlodipine.**

Lomitapide: The risk of myopathy/rhabdomyolysis may be increased by concomitant administration of lomitapide (see DOSAGE AND ADMINISTRATION; WARNINGS AND PRECAUTIONS, Muscle Effects, Other Drugs).

Moderate Inhibitors of CYP3A4: Patients taking other medicines labeled as having a moderate inhibitory effect on CYP3A4 concomitantly with simvastatin, particularly higher simvastatin doses, may have an increased risk of myopathy. When coadministering simvastatin with a moderate inhibitor of CYP3A4, a dose adjustment of simvastatin may be necessary.

Transport Protein Inhibitors: Simvastatin acid is a substrate of OATP1B1 (organic anion-transporting polypeptide1B1) and, therefore, concomitant administration of medicinal products that are inhibitors of OATP1B1 may lead to an increase in plasma concentration of simvastatin and increase the risk of myopathy.

Evidence has also been obtained with other statins that concurrent use of statins and inhibitors of Breast Cancer Resistance Protein such as elbasvir and grazoprevir increased the plasma concentration of these statins. A dose adjustment of simvastatin may be necessary. It is suggested that the dose of simvastatin should not exceed 20 mg daily in such patients (see WARNINGS AND PRECAUTIONS).

Niacin (nicotinic acid) (≥1 g/day): Myopathy, including rhabdomyolysis, has occurred in patients who were receiving co-administration of simvastatin or other HMG-CoA reductase inhibitors with niacin, particularly in subjects with pre-existing renal insufficiency. In a clinical trial (median follow-up 3.9 years) involving patients at high risk of cardiovascular disease and with well-controlled LDL-C levels on simvastatin 40 mg/day with or without ezetimibe 10 mg, there was no incremental benefit on cardiovascular outcomes with the addition of lipid-modifying doses (≥1 g/day) of niacin. Therefore, the benefit of the combined use of simvastatin with niacin should be carefully weighed against the potential risks of the combination. In addition, in this trial, the incidence of myopathy was approximately 0.24% for Chinese patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg compared with 1.24% for Chinese patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg coadministered with extended-release niacin/laropiprant 2 g/40 mg. **While the only Asian population assessed in this clinical trial was Chinese, and the incidence of myopathy is higher in Chinese than in non-Chinese patients, coadministration of simvastatin with lipid-modifying doses (≥1 g/day) of niacin is not recommended in Asian patients.**

Daptomycin: MYLAN-SIMVASTATIN should be temporarily suspended in patients taking daptomycin particularly those with pre-disposing factors for myopathy/rhabdomyolysis (see WARNINGS AND PRECAUTIONS, Muscle Effects)

Colchicine: There have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and simvastatin in patients with renal insufficiency. Close clinical monitoring of such patients taking this combination is advised.

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.

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

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

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, because larger quantities significantly increase the plasma levels of HMG-CoA reductase inhibitory activity, grapefruit juice should be avoided during simvastatin therapy.

Drug-Laboratory Interactions

Simvastatin may elevate serum transaminase and creatine phosphokinase levels (from skeletal muscles). Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate

myopathy (see WARNINGS AND PRECAUTIONS, Muscle Effects and ADVERSE REACTIONS, Laboratory Tests).

Prescribing recommendations for interacting agents are summarized in the table below (see also CONTRAINDICATIONS; DETAILED PHARMACOLOGY, Pharmacokinetics).

Table 1 - Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Potent CYP3A4 inhibitors e.g.: Itraconazole Ketoconazole Posaconazole Voriconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Boceprevir Telaprevir Nefazodone Cobicistat Cyclosporine Danazol Gemfibrozil	Contraindicated with simvastatin
Other fibrates (except fenofibrate) Verapamil Diltiazem	Do not exceed 10 mg simvastatin daily
Elbasvir Grazoprevir Amiodarone Amlodipine	Do not exceed 20 mg simvastatin daily
Fusidic acid	Is not recommended with simvastatin
Niacin (≥ 1 g/day)	For Asian patients, not recommended with simvastatin
Lomitapide	For HoFH patients who have been taking 80 mg/day simvastatin chronically without evidence of muscle toxicity do not exceed 40 mg simvastatin daily. For all other HoFH patients do not exceed 20 mg/day simvastatin
Daptomycin	Simvastatin should be temporarily suspended in patients taking daptomycin particularly those with pre-disposing factors for myopathy/rhabdomyolysis
Grapefruit juice	Avoid grapefruit juice

DOSAGE AND ADMINISTRATION

Patients should be placed on a standard cholesterol-lowering diet before receiving MYLAN-SIMVASTATIN, and should continue on this diet during treatment with MYLAN-

SIMVASTATIN. If appropriate, a program of weight control and physical exercise should be implemented.

Prior to initiating therapy with MYLAN-SIMVASTATIN, secondary causes for elevations in plasma lipid levels should be excluded. A lipid profile should also be performed.

Recommended Dose and Dosage Adjustment
The usual dosage is 5 to 40 mg/day. **Due to the increased risk of myopathy/rhabdomyolysis, particularly during the first year of treatment, the use of 80 mg/day of MYLAN-SIMVASTATIN is discouraged (see WARNINGS AND PRECAUTIONS, Muscle Effects). Therefore, 80 mg/day of MYLAN-SIMVASTATIN should be restricted to patients who have been taking this dosage chronically with no evidence of muscle toxicity or to patients at high risk for cardiovascular complications who do not tolerate other statins and in whom the benefits are expected to outweigh the potential risks.** In other patients, consider alternative treatment strategies as follows:

- Patients unable to achieve their LDL-C goal with the 40-mg dose of MYLAN-SIMVASTATIN should be switched to alternative LDL-C-lowering treatments with lower risks of muscle toxicity.

- Patients currently tolerating 80 mg/day of MYLAN-SIMVASTATIN who need an interacting drug that is either contraindicated or associated with an increase of plasma level of MYLAN-SIMVASTATIN should be switched to an alternative statin with less potential for a drug-drug interaction.

Homozygous familial hypercholesterolemia
In HoFH patients taking lomitapide concomitantly with simvastatin, the dose of simvastatin should not exceed 20 mg/day (or 40 mg/day in those HoFH patients who have been taking 80 mg of simvastatin chronically without evidence of muscle toxicity) (see WARNINGS AND PRECAUTIONS, Muscle Effects and DRUG INTERACTIONS).

Hyperlipidemia
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 MYLAN-SIMVASTATIN. Adjustments of dosage, if required, should be made as specified above.

Dosage in Pediatric Patients (10-17 years of age) with Heterozygous Familial Hypercholesterolemia
The recommended usual starting dose is 10 mg once a day in the evening. The recommended dosing range is 10-40 mg/day; the maximum recommended dose is 40 mg/day. Doses should be individualized according to the recommended goal of therapy (see ACTION AND CLINICAL PHARMACOLOGY).

Prevention of Cardiovascular Disease
The usual starting dose of MYLAN-SIMVASTATIN is 40 mg/day given as a single dose in the evening 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.

Dosing Considerations in Special Populations

Renal Impairment
Because MYLAN-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 MYLAN-SIMVASTATIN is administered to patients with severe renal insufficiency; such patients should be started at 5mg/day of simvastatin and be closely monitored (see WARNINGS AND PRECAUTIONS, Muscle Effects and Renal).

Hepatic Impairment
MYLAN-SIMVASTATIN is contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Concomitant Therapy
See WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS.

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

A few cases of overdosage 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

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

After oral ingestion, MYLAN-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

MYLAN-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

MYLAN-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

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

MYLAN-SIMVASTATIN 5 mg tablets, are buff coloured, shield shaped, film coated tablets, with “SM” over “5” on one side and “G” on the other. Available in HDPE bottles of 100 tablets.

MYLAN-SIMVASTATIN 10 mg tablets, are peach coloured, shield shaped, film coated tablets, with “SM” over “10” on one side and “G” on the other. Available in blister packages of 30 tablets and HDPE bottles of 100 tablets.

MYLAN-SIMVASTATIN 20 mg tablets, are tan coloured, shield shaped, film coated tablets, with “SM” over “20”on one side and “G” on the other. Available in blister packages of 30 tablets and in HDPE bottles of 100 tablets.

MYLAN-SIMVASTATIN 40 mg tablets, are pink to brick red coloured, shield shaped, film coated tablets, with “SM” over “40” on one side and “G” on the other. Available in blister packages of 30 tablets and HDPE bottles of 100 tablets.

MYLAN-SIMVASTATIN 80 mg tablets, are brick red coloured, capsule-shaped, film coated tablets, with “SM80” on one side and “G” on the other. Available in HDPE bottles of 100 tablets.

Non-medicinal ingredients: ascorbic acid, butylated hydroxyanisole, citric acid, dehydrated alcohol, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, talc and titanium dioxide. Tablets 5 mg also contain polydextrose. Tablets 5, 10, 40 and 80 mg contain triacetin. Tablets 5 and 20 mg contain polyethylene glycol. Tablets 5, 10, 20, 40 and 80 mg contain red iron oxide. Tablets 5, 10 and 20 mg contain yellow iron oxide. Tablets 20 mg contain black iron oxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

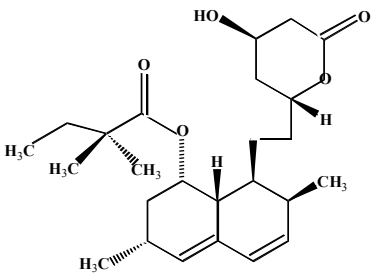
Proper name: Simvastatin

Chemical name: 1) Butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1α,3α,7β,8β(2S*,4S*),8aβ]].

2) 2,2-Dimethylbutyric acid, 8-ester with (4R,6R)-6-[2-[(1S,2S,6R,8S,8αR)-1,2,6,7,8,8a-hexahydro-8-hydroxy-2,6-dimethyl-1-naphthyl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

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

Structural Formula:



Molecular weight: 418.57 g/mol

Description: Simvastatin is a white to off-white crystalline powder.

Solubilities: Simvastatin is insoluble in water, but is soluble in polar organic solvents. Simvastatin is very soluble in acetone, methanol, ethanol and slightly soluble in cyclohexane. Solubility data obtained at room temperature are tabulated below:

Solvent	Solubility (mg/mL)
Chloroform	610
Dimethyl sulfoxide	540
Methanol	200
Ethanol	160
n-Hexane	0.15
Hydrochloric acid, 0.1M	0.06*
Polyethylene glycol 400	70
Propylene glycol	30
Sodium hydroxide, 0.1M	70**
Water	0

NB: Hydrolysis of the lactone moiety of the molecule occurs in acid and alkaline media. Solubility data are therefore for the free hydroxy acid* and the sodium salt of the hydroxy acid** of simvastatin.

Partition co-efficient: At room temperature, the partition co-efficient of simvastatin (K, o/w) between octan-1-ol and either pH 4 acetate or pH 7.2 acetate buffer is > 1995.

CLINICAL TRIALS

Comparative Bioavailability Studies

Two bioequivalence studies were performed comparing MYLAN-SIMVASTATIN tablets against the Canadian Reference Product ZOCOR® tablets, one with 80mg tablets, the other with 20mg tablets. Both studies were randomized, 2-period, 2-sequence, single-dose, crossover, fasted, comparative bioavailability studies. The pharmacokinetic data are presented in the following tables.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA (1 X 80 MG TABLET)

SIMVASTATIN FROM MEASURED AND LOG TRANSFORMED DATA UNCORRECTED FOR POTENCY

PARAMETER	GEOMETRIC LS MEAN ARITHMETIC MEAN (CV%)		% RATIO OF GEOMETRIC MEANS	90% CONFIDENCE INTERVAL
	TEST MYLAN-SIMVASTATIN	REFERENCE ZOCOR †		
AUC_T (ng.h/mL)	69.89 77.58 (43.0)	63.64 70.72 (46.3)	109.83	99.84 - 120.81
AUC_I (ng.h/mL)	80.68 90.90 (46.8)	72.03 81.15 (48.4)	112.01	100.50 - 124.84
C_{MAX} (ng/mL)	12.70 15.08 (59.9)	14.94 18.13 (64.3)	84.97	76.85 - 93.96
T_{MAX}* (h)	2.00 (86.3)	1.73 (79.9)		
$T_{1/2}$* (h)	7.99 (47.0)	8.33 (42.5)		

* expressed as arithmetic mean (CV%) only.
† Canadian brand leader ZOCOR, manufactured by Merck Frosst Canada & Co., Kirkland, QC, Canada.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA (2 X 20 MG TABLET)				
SIMVASTATIN FROM MEASURED AND LOG TRANSFORMED DATA UNCORRECTED FOR POTENCY				
PARAMETER	**GEOMETRIC LS MEAN ARITHMETIC MEAN (CV%)**		**% RATIO OF GEOMETRIC MEANS**	**90% CONFIDENCE INTERVAL**
	TEST MYLAN-SIMVASTATIN	**REFERENCE ZOCOR †**		
AUC_T (ng.h/mL)	29.933 34.218 (62.3)	28.186 32.969 (60.4)	106.20	97.04 - 116.22
AUC_I (ng.h/mL)	32.202 36.850 (61.6)	30.292 36.542 (71.3)	106.31	96.34 - 117.30
C_{MAX} (ng/mL)	7.431 8.347 (49.0)	7.736 8.771 (50.3)	96.07	87.41 - 105.57
T_{MAX}* (h)	1.72 (77.4)	1.54 (75.1)		
$T_{1/2}$* (h)	6.00 (47.6)	5.52 (75.3)		
* expressed as arithmetic mean (CV%) only † Canadian brand leader ZOCOR, manufactured by Merck Frosst Canada & Co., Kirkland, QC, Canada.				

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 2), 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 2 – 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 3:

Table 3 – 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)
Lower Dose Comparative Study					
Simvastatin - 5 mg*	109	-19	-26	10	-12
- 10 mg*	110	-23	-30	12	-15
Scandinavian Simvastatin Survival Study					
Placebo	2223	-1	-1	0	-2
Simvastatin - 20 mg*	2221	-28	-38	8	-19
Upper Dose Comparative Study					
Simvastatin - 40 mg*	433	-31	-41	9	-18
- 80 mg*	664	-36	-47	8	-24
Multicenter Combined Hyperlipidemia Study					
Placebo	125	1	2	3	-4
Simvastatin - 40 mg*	123	-25	-29	13	-28
- 80 mg*	124	-31	-36	16	-33

* In the evening

One third of patients obtained a reduction in LDL-cholesterol of 53% or more at the 80 mg dose. The percent reduction in LDL-cholesterol was essentially independent of the baseline level. In contrast, the percent reduction in triglycerides was related to the baseline level of triglycerides. Of the 664 patients randomized to 80 mg, 475 patients with plasma triglycerides ≤ 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 3. 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 lV 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 4.

Table 4 – Simvastatin in FH and NON-FH Patients (Percent Change from Baseline after 12 Weeks)

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

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

Simvastatin was compared to cholestyramine, or gemfibrozil respectively, in double-blind parallel studies. All studies were performed in patients who exhibited moderate to high hypercholesterolemia and thus were thought to be at higher than average risk of coronary events. Results of these studies are summarized in Tables 5, 6, 7.

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)	**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 6 – Simvastatin vs. Cholestyramine (Percent Change from Baseline after 12 Weeks)

TREATMENT	**N**	**TOTAL-C** (mean)	**LDL-C** (mean)	**HDL-C** (mean)	**LDL-C /HDL-C** (mean)	**TOTAL-C /HDL-C** (mean)	**TG** (mean)
Simvastatin 20 and 40 mg q.p.m.	177	-33	-41	+15	-46	-39	-10
Cholestyramine 4 to 12 g b.i.d.	84	-21	-30	+10	-35	-26	+36

Table 7 – 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 5.5-8.0 mmol/L (212-309 mg/dL). In this multicenter, randomized, double-blind, placebo-controlled study, patients with angina or a previous myocardial infarction (MI) were treated with diet and standard care and either simvastatin 20-40 mg daily (n=2221) or placebo (n=2223) for a median duration of 5.4 years. Over the course of the study, treatment with simvastatin led to mean reductions in total cholesterol, LDL-cholesterol, and triglycerides of 25%, 35%, and 10%, respectively, and a mean increase in HDL-cholesterol of 8%. Simvastatin reduced the risk of death (Figure 1) by 30%, p=0.0003 (182 deaths in the simvastatin group vs 256 deaths in the placebo group). The risk of CHD death was reduced by 42% (111 vs 189). Simvastatin also decreased the risk of having major coronary events (CHD death plus hospital-verified and silent non-fatal MI) (Figure 2) by 34%, p<0.00001 (431 patients vs 622 patients with one or more events). The risk of having a hospital-verified non-fatal MI was reduced by 37%. Simvastatin reduced the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37%, p<0.00001 (252 patients vs 383 patients). Furthermore, posthoc analyses indicate that simvastatin reduced the risk of fatal plus non-fatal cerebrovascular events (stroke and transient ischemic attacks) by 28% (75 patients vs 102 patients). Following the same kind of analyses, in hypercholesterolemic patients with diabetes mellitus, the risk of major coronary events was reduced by 55% (24 patients vs 44 patients). There was no statistically significant difference between groups in non-cardiovascular mortality. Simvastatin reduced the risk of major coronary events to a similar extent across the range of baseline total and LDL-cholesterol levels. The risk of death in patients ≥ 60 years of age was decreased by 27% and in patients <60 years of age by 37% (p < 0.01 in both age groups).

Figure 1

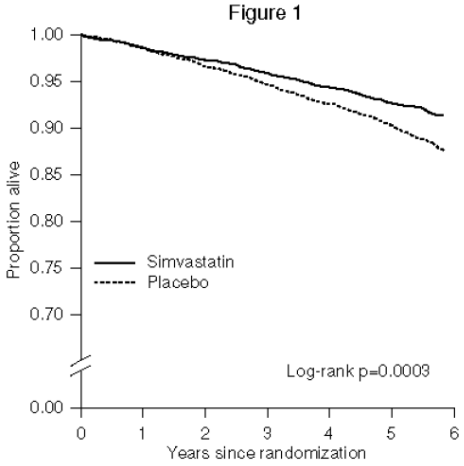
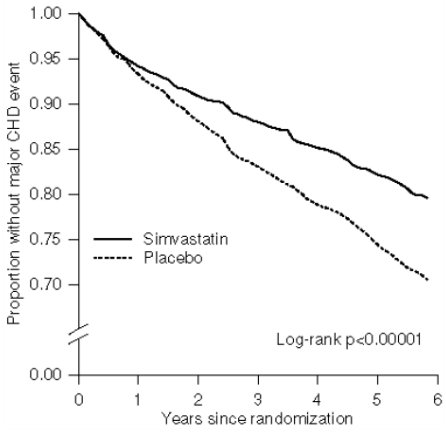


Figure 2



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

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

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

Because there were only 57 deaths among the patients with **angina** alone at baseline and 53 deaths among **female** patients, the effect of simvastatin on mortality in these subgroups could not be adequately assessed. However, trends in reduced coronary mortality and in major coronary events were consistent between these subgroups and the total study cohort.
The Heart Protection Study (HPS) was a large, multi-center, randomized, placebo-controlled, double-blind study with a mean duration of 5 years conducted in 20,536 patients (10,269 on simvastatin 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 8). 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).

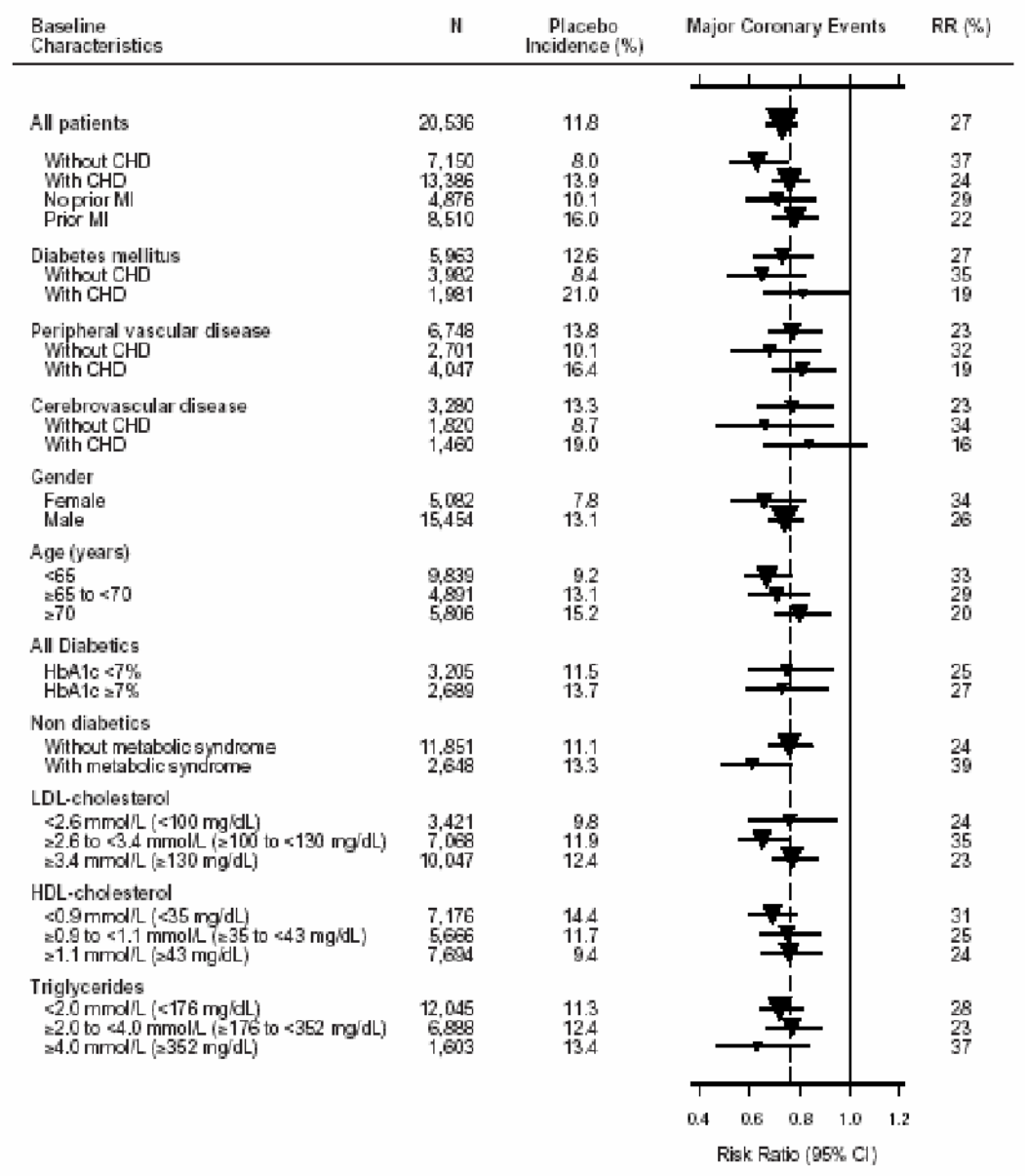
Table 8 – Summary of Results of HPS

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 5.5 to 8.0 mmol/L (212 to 308 mg/dL) and a mean baseline LDL value of 4.4 mmol/L (170 mg/dL) 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

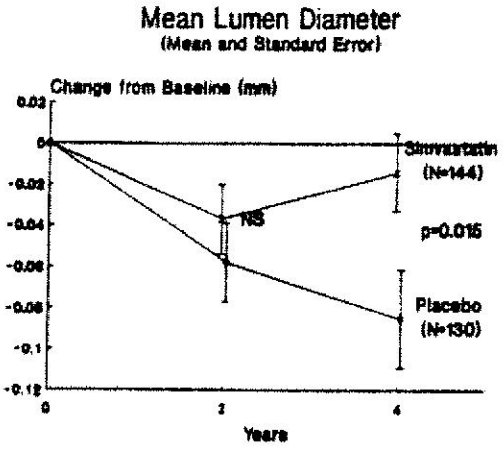
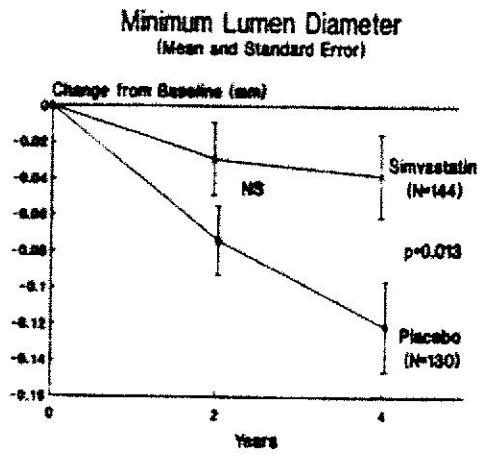


Figure 5



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.

Clinical Trials in Pediatric Patients (10-17 years of age)

In a double-blind, placebo-controlled study, 175 patients (99 adolescent boys and 76 post-menarchal girls) 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia were randomized to simvastatin or placebo for 24 weeks (base study). Inclusion in the study required a baseline LDL-C level between 4.14 and 10.36 mmol/L (160 and 400 mg/dL) and at least one parent with an LDL-C level >4.90 mmol/L (189 mg/dL). The dosage of simvastatin (once daily in the evening) was 10 mg for the first 8 weeks, 20 mg for the second

8 weeks, and 40 mg thereafter. In a 24-week extension, 144 patients elected to continue therapy and received simvastatin 40 mg or placebo.

Simvastatin significantly decreased plasma levels of total-C, LDL-C, TG, and Apo B (see Table 9). Results from the extension at 48 weeks were comparable to those observed in the base study.

After 24 weeks of treatment, the mean achieved LDL-C value was 3.24 mmol/L (124.9 mg/dL) range: 1.66-7.49 mmol/L (64.0-289.0 mg/dL) in the simvastatin 40 mg group compared to 5.38 mmol/L (207.8 mg/dL) range: 3.32-8.65 mmol/L (128.0-334.0 mg/dL) in the placebo group.

The safety and efficacy of doses above 40 mg daily have not been studied in children with heterozygous familial hypercholesterolemia. The long-term efficacy of simvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

Table 9 – Lipid-lowering Effects of Simvastatin in Adolescent Patients with Heterozygous Familial Hypercholesterolemia after 24 Weeks of Treatment

Treatment	N		TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	TG (median)	ApoB (mean)
Placebo	67	% Change from Baseline	+1.6	+1.1	+3.6	-3.2	-0.5
		(95% CI)	(-2.2, 5.3)	(-3.4, 5.5)	(-0.7, 8.0)	(-11.8, 5.4)	(-4.7, 3.6)
		Mean baseline, mmol/L [mg/dL]	7.24 [278.6]	5.49 [211.9]	1.21 [46.9]	1.02 [90.0]	1.86g/L [186.3]
Simvastatin	106	% Change from Baseline	-26.5	-36.8	+8.3	-7.9	-32.4
		(95% CI)	(-29.6, -23.3)	(-40.5, -33.0)	(4.6, 11.9)	(-15.8, 0.0)	(-35.9, -29.0)
		Mean baseline, mmol/L [mg/dL]	7.03 [270.2]	5.28 [203.8]	1.24 [47.7]	0.88 [78.3]	1.80 g/L [179.9]

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 2-6 under CLINICAL TRIALS).

The active ß-hydroxyacid form of simvastatin is a specific, reversible, inhibitor of HMG-CoA reductase, the enzyme which catalyzes the conversion of HMG-CoA to mevalonate. However, at therapeutic doses, the enzyme is not completely blocked, thereby allowing biologically necessary amounts of mevalonate to be available. Because the conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol, therapy with MYLAN-SIMVASTATIN would not be expected to cause an accumulation of potentially toxic sterols. In addition, HMG-CoA is metabolized readily back to acetyl-CoA, which participates in many biosynthetic processes in the body.

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

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

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

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

Both simvastatin and its ß-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 ß-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 and/or OATP1B1 (see CONTRAINDICATIONS).

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 (see WARNINGS AND PRECAUTIONS, Muscle Effects and DRUG INTERACTIONS).

In a pharmacokinetic study, concomitant administration of amlodipine caused a 1.6-fold increase in exposure of simvastatin acid (see WARNINGS AND PRECAUTIONS, Muscle Effects and DRUG INTERACTIONS).

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. (see WARNINGS AND PRECAUTIONS, Muscle Effects and DRUG INTERACTIONS).

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 CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Muscle Effects and DRUG INTERACTIONS).

Animal Pharmacology

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

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

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

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

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

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

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

In another study, five chow-fed dogs received 8 mg/kg/day p.o. of simvastatin in their diet for a period of 24 days. Total cholesterol and LDL-cholesterol decreased by an average of 26.2% and

62% respectively. HDL-cholesterol levels decreased slightly but the decrease was not considered significant.

Pharmacokinetics:

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

Absorption of simvastatin, estimated relative to an intravenous reference dose, in rats and dogs, averaged about 85% of an oral dose. Studies in the dog have indicated that the availability of the absorbed drug to the general circulation is limited by extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of simvastatin, the availability of drug to the general circulation is low.

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

Only in mice and rats is there evidence that a metabolite of simvastatin is formed by ß-oxidation. Biliary excretion is the major route of elimination of the metabolites of simvastatin.
In dogs, 74% of the radioactivity of an oral dose of ^{14}C-simvastatin was recovered in the feces and 11% in the urine.

TOXICOLOGY

Table 10 - 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 11 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 11 – 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 12 – 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 13 – 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/m^2 body surface area) has been shown to reduce the fetal plasma levels of mevalonate.

REFERENCES

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

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

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

4. Chaudron JM, Luwaert R. Effects of simvastatin on plasma lipids in coronary patients with severe hypercholesterolaemia. Acta Cardiol 1989;44:48-9.

5. Collins R, Armitage J, Parish S, Sleight P, Peto R. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomized placebo-controlled trial. Lancet 2002; 360:7-22.

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

7. Davidson MH, Stein EA, Dujovne CA, Hunninghake DB, Weiss SR, Knopp RH, Illingworth DR, Mitchel YB, Melino MR, Zupkis RV, Dobrinska MR, Amin RD, Tobert JA. The efficacy and six-week tolerability of simvastatin 80 and 160 mg/day. Am J Cardiol 1997;79:38-42.

8. Erkelens DW, Baggen MG, Van Doormaal JJ, Kettner M, Koningsberger JC, Mol MJ. Clinical experience with simvastatin compared with cholestyramine. Drugs 1988;36(Suppl 3):87-92.

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

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

11. Ghirlanda G, Oradei A, Manto A, Lippa S, Uccioli L, Caputo S, Greco AV, Littarru GP. Evidence of plasma CoQ_{10}-lowering effect by HMG-CoA reductase inhibitors: a double-blind, placebo-controlled study. J Clin Pharmacol 1993;33:226-9.

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

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

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

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

16. Kjekshus J, Pederson TR, Olsson AG, Faergeman O, Pyörälä K. The effects of simvastatin on the incidence of heart failure in patients with coronary heart disease. J Card Fail 1997;3:249-54.

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

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

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

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

21. Meier C, Stey C, Brack T, Maggiorini M, Risti B, Krahenbuehl S. Rhabdomyolysis in patients treated with simvastatin and cyclosporin: role of hepatic cytochrome P 450 system activity. Schweiz Med Wochenschr 1995;25:1342-6.

22. Miettinen TA, Pyörälä K, Olsson AG, Musliner TA, Cook TJ, Faergeman O, Berg K, Pedersen T, Kjekshus J. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris: Findings from the Scandinavian Simvastatin Survival Study (4S). Circulation 1997;96(12): 4211-8.

23. Mol MJTM, Erkelens DW, Gevers Leuven JA, Schouten JA, Stalenhoef AFH. Effects of synvinolin (MK-733) on plasma lipids in familial hypercholesterolaemia. Lancet 1986;II(8513):936-9.

24. Pedersen TR, Berg K, Cook TJ, Faergeman O, Haghfelt T, Kjekshus J, Miettinen T, Musliner TA, Olsson AG, Pyörälä K, Thorgeirsson G, Tobert JA, Wedel H, Wilhelmsen L. Safety and tolerability of cholesterol lowering with simvastatin during 5 years in the Scandinavian Simvastatin Survival Study. Arch Intern Med 1996;156:2085-92.

25. Pedersen TR, Kjekshus J, Pyörälä K, Olsson AG, Cook TJ, Musliner TA, Tobert JA, Haghfelt T. Effect of simvastatin on ischemic signs and symptoms in the Scandinavian Simvastatin Survival Study (4S). Am J Cardiol 1998; 81:333-5.

26. Phan T, McLeod JG, Pollard JD, Peiris O, Rohan A, Halpern JP. Peripheral neuropathy associated with simvastatin. J Neurol Neurosurg Psychiatry 1995;58:625-8.

27. Pyörälä K, Pedersen TR, Kjekshus J, Faerceman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. Diabetes Care 1997;20(4):614-20.

28. Quérin S, Lambert R, Cusson JR, Grégoire S, Vickers S, Stubbs RJ, Sweany AE, Larochelle P. Single-dose pharmacokinetics of ^{14}C-lovastatin in chronic renal failure. Clin Pharmacol Ther 1991;50:437-41.

29. Rabelink AJ, Hene RJ, Erkelens DW, Joles JA, Koomans HA. Effects of simvastatin and cholestyramine on lipoprotein profile in hyperlipidaemia of nephrotic syndrome. Lancet 1988;II(8624):1335-8.

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

31. SEARCH Study Collaborative Group Oxford UK. Randomised comparison of more intensive LDL-lowering therapy with 80 mg versus 20 mg simvastatin daily in 12,064 myocardial infarction survivors, 2010. Lancet 2010; 376: 1658–69.

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

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

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

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

36. Stein E, Kreisberg R, Miller V, Mantell G, Washington L, Shapiro DR, Multicenter Group I. Effects of simvastatin and cholestyramine in familial and non-familial hypercholesterolemia. Arch Int Med 1990;150:341-5.

37. Stein E, Plotkin D, Bays H, Davidson M, Dujovne C, Korenman S, Stepanavage M, Mercuri M. Effects of simvastatin (40 and 80 mg/day) in patients with mixed hyperlipidemia. Am J Cardiol 2000;86(4):406-11.

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

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

40. Tobert JA, Leslie BR, Schaefer EJ, Van Buuren HR, Baggen MGA, Wilson JHP, Grundy SM. HMG-CoA reductase inhibitors for hypercholesterolemia. N Engl J Med 1988;319:1222-3.

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

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

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

44. Product Monograph for ZOCOR® by Merck Canada Inc. date of revision August 10, 2018 (Control No. 215663).

45. Product Monograph for ZOCOR® by Merck Canada Inc. date of revision May 24, 2019 (Control No. 224707).

PART III: CONSUMER INFORMATION

[Pr]MYLAN-SIMVASTATIN
Simvastatin tablets, USP

This leaflet is part III of a three-part "Product Monograph" published when MYLAN-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 MYLAN-SIMVASTATIN. Contact your doctor, nurse 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

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

What the medication is used for:
Your doctor has prescribed MYLAN-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), MYLAN-SIMVASTATIN should lessen the risk of heart attack or stroke.

You can also benefit from taking MYLAN-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 doctor, nurse or pharmacist may recommend a diet to reduce cholesterol and other measures such as exercise and weight control.

Safety and effectiveness have been studied in 10-17 year old boys and in girls, who had started their menstrual period at least one year before (see Proper Use of this Medication). Simvastatin has not been studied in children under the age of 10 years. For more information, talk to your doctor, nurse or pharmacist.

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.

MYLAN-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 MYLAN-SIMVASTATIN if you are:

- allergic to simvastatin or any non-medicinal ingredient in the formulation
- diagnosed with active liver disease
- pregnant or breast-feeding
- taking any of the following medicines:
  - certain antifungal medicines (such as itraconazole, ketoconazole, posaconazole or voriconazole)
  - HIV protease inhibitors (such as indinavir, nelfinavir, ritonavir, and saquinavir)
  - certain hepatitis C virus protease inhibitors (such as boceprevir or telaprevir)
  - certain antibiotics (such as erythromycin, clarithromycin, or telithromycin)
  - antidepressant nefazodone
  - medicines containing cobicistat
  - gemfibrozil (a fibric acid medicine for lowering cholesterol)
  - cyclosporine
  - danazol.

Ask your doctor, nurse or pharmacist if you are not sure if your medicine is listed above.

What the medicinal ingredient is:
Simvastatin

What the nonmedicinal ingredients are:
Ascorbic acid, butylated hydroxyanisole, citric acid, dehydrated alcohol, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, talc and titanium dioxide. Tablets 5 mg contain polydextrose; 5, 10, 40 and 80 mg - triacetin; 5 and 20 mg - polyethylene glycol; 5, 10, 20, 40 and 80 mg - red iron oxide; 5, 10 and 20 mg - yellow iron oxide; 20 mg - black iron 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 MYLAN-SIMVASTATIN, tell your doctor, nurse 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, fluvastatin, lovastatin, pravastatin or rosuvastatin, or have developed an allergy or intolerance to them
- have kidney or liver problems
- have diabetes. Slightly increased blood sugar can occur when you take simvastatin. Discuss with your doctor, nurse or pharmacist your risk of developing 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 doctor, nurse or pharmacist the potential hazards to the fetus and the importance of birth control methods.
- become pregnant. MYLAN-SIMVASTATIN should not be used by pregnant women. If you become pregnant, discontinue use immediately and discuss with your doctor, nurse or pharmacist.
- are Asian.

When starting or increasing the dose of MYLAN-SIMVASTATIN, or at any time, if you experience any unexplained muscle pain, tenderness or weakness, you must report promptly to your doctor, nurse or pharmacist.

Be sure to tell your doctor, nurse or pharmacist you are taking MYLAN-SIMVASTATIN before undergoing any major elective surgery or if you have any other new major medical issues.

INTERACTIONS WITH THIS MEDICATION

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

Because taking MYLAN-SIMVASTATIN with any of the following drugs or substances 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 doctor, nurse or pharmacist if you are taking:

- antifungal agents (such as itraconazole, ketoconazole, posaconazole or voriconazole)
- HIV protease inhibitors (such as indinavir, nelfinavir, ritonavir, and saquinavir)
- Hepatitis C antiviral agents (such as boceprevir, telaprevir, elbasvir or grazoprevir)
- the antibiotics erythromycin, clarithromycin, telithromycin, and fusidic acid (intravenous or oral)
- the antidepressant nefazodone
- medicines containing cobicistat
- cyclosporine (immunosuppressant)
- danazol
- fibrates/fibric acid derivatives (bezafibrate and gemfibrozil) (drug to treat lipids problems)
- 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)
- lomitapide (a drug used to treat a serious and rare genetic cholesterol condition)
- daptomycin (a drug used to treat complicated skin and skin structure infections and bacterial infections in the blood, including certain heart valve infections)
- grapefruit juice (which should be avoided while taking simvastatin).

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

Some of these have already been listed in the above section "When it should not be used".

PROPER USE OF THIS MEDICATION

Usual Dose:

- Take your medication exactly as your doctor, nurse or pharmacist instructed. Do not change the dose unless directed by your doctor. It is usually recommended to be taken with the evening meal. Because of the increased risk of muscle problems, taking 80 mg each day is only recommended for patients who have been taking this amount for a long time with no muscle problems or for patients at high risk of heart disease problems who have problems taking other statins. It is important to continue taking the tablets as instructed. **Do not alter the dosage or stop taking the medicine without consulting your doctor, nurse or pharmacist.**
- For children (10-17 years old), the recommended usual starting dose is 10 mg a day in the evening. The maximum recommended dose is 40 mg a day.
- Carefully follow any measures that your doctor, nurse or pharmacist has recommended for diet, exercise or weight control.

- When taking MYLAN-SIMVASTATIN, you should avoid consuming grapefruit juice.
- When taking MYLAN-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 doctor, nurse or pharmacist 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 doctor, nurse or pharmacist.
- Let your doctor, nurse or pharmacist know if you suffer a severe injury, or severe infection.
- If you have to undergo any kind of surgery, tell your doctor, nurse or pharmacist about the planned surgery; and also inform the doctor in charge that you are taking this medicine.

Overdose:

If you think you have taken too much MYLAN-SIMVASTATIN, contact your healthcare professional, hospital emergency department or regional Poison Control Centre 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.

The following side effects that may occur, generally do not require medical attention, and may come and go during treatment. If any of the following persist or become troublesome, **do check with your doctor, nurse or pharmacist:**

Constipation, diarrhea, gas, stomach upset, nausea
Pain in the abdomen
Headache
Skin rash
Poor memory
Memory loss
Confusion
Trouble sleeping
Depression
Erectile dysfunction
Breathing problems including persistent cough and/or shortness of breath or fever.

Possible side effects reported with other statins:
Sleep disturbances, including nightmares.

Side effects such as myalgia (muscle pain), myopathy (muscle disease with aching or weakness) [that in very rare cases may not go away after stopping MYLAN-SIMVASTATIN], rhabdomyolysis (a muscle wasting disease or muscle breakdown), associated tenderness, and rare cases of muscle breakdown resulting in kidney damage that can lead to death have been reported with other drugs of this class, known as HMG-CoA reductase inhibitors ("statins"), including MYLAN-SIMVASTATIN. This risk of muscle breakdown is greater for patients taking higher doses of MYLAN-SIMVASTATIN, particularly the 80 mg dose. This risk of muscle breakdown is also greater for older patients (65 years of age and older), female patients, patients with abnormal kidney function, and patients with thyroid problems.

See your doctor regularly to check your cholesterol level and to check for side effects. Your doctor should do blood tests to check your liver before you start taking MYLAN-SIMVASTATIN and if you have any symptoms of liver problems while you take MYLAN-SIMVASTATIN.

MYLAN-SIMVASTATIN can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Unknown	**Increased blood sugar:** frequent urination, thirst and hunger	✓		
Rare	**Allergic reactions:** swelling of the face, eyelids, lips, tongue and/or throat that may cause difficulty in swallowing, sudden shortness of breath, flushing, sensitivity to light, skin reactions including hives			✓
	Brownish or discoloured urine		✓	
	Liver Disorder: belly pain, dark urine, itchy skin, nausea or vomiting, loss of appetite, pale stools, yellowing of skin or the whites of your eyes.			✓
	Generalized weakness, especially if you do not feel well or have a fever		✓	
	Unexplained muscle pain		✓	
	Muscle tenderness or muscle weakness		✓	
	Blurred vision		✓	

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

HOW TO STORE IT

Store your tablets at room temperature (15ºC - 30ºC), 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 and sight of children.

Do not use outdated medicine.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax, or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about MYLAN-SIMVASATIN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); or by calling Mylan Pharmaceuticals ULC at 1-844-596-9526

To report an adverse event related to MYLAN-SIMVASTATIN, please contact 1-844-596-9526

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