



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use simvastatin safely and effectively. See full prescribing information for simvastatin.

Simvastatin Tablets, USP

Initial U.S. Approval: 1991

RECENT MAJOR CHANGES

Table with 2 columns: Change and Date. Includes Dosage and Administration, Contraindications, Warnings and Precautions, and Indications and Usage.

INDICATIONS AND USAGE

Simvastatin tablets are an HMG-CoA reductase inhibitor (statin) indicated as an adjunctive therapy to diet to:

- Reduce the risk of total mortality by reducing CHD deaths and reduce the risk of non-fatal myocardial infarction, stroke, and the need for revascularization procedures in patients at high risk of coronary events. (1.1)
Reduce elevated total-C, LDL-C, Apo B, TG and increase HDL-C in patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia. (1.2)
Reduce elevated TG in patients with hypertriglyceridemia and reduce TG and VLDL-C in patients with primary dysbetalipoproteinemia. (1.2)
Reduce total-C and LDL-C in adult patients with homozygous familial hypercholesterolemia. (1.2)
Reduce elevated total-C, LDL-C, and Apo B in boys and postmenarchal girls, 10 to 17 years of age with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy. (1.2, 1.3)

Limitations of Use

Simvastatin tablets have not been studied in Fredrickson Types I and V dyslipidemias.(1.4)

DOSAGE AND ADMINISTRATION

- Dose range is 5 to 40 mg/day. (2.1)
Recommended usual starting dose is 10 or 20 mg once a day in the evening. (2.1)
Recommended starting dose for patients at high risk of CHD is 40 mg/day. (2.1)
Due to the increased risk of myopathy, including rhabdomyolysis, use of the 80 mg dose of simvastatin should be restricted to patients who have been taking simvastatin 80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity. (2.2)
Patients who are currently tolerating the 80 mg dose of simvastatin who need to be initiated on an interacting drug that is contraindicated or is associated with a dose cap for simvastatin should be switched to an alternative statin with less potential for the drug-drug interaction. (2.2)
Due to the increased risk of myopathy, including rhabdomyolysis, associated with the 80 mg dose of simvastatin, patients unable to achieve their LDL-C goal utilizing the 40 mg dose of simvastatin should not be titrated to the 80 mg dose, but should be placed on alternative LDL-C-lowering treatment(s) that provides greater LDL-C lowering. (2.2)
Adolescents (10 to 17 years of age) with HeFH: starting dose is 10 mg/day; maximum recommended dose is 40 mg/day. (2.5)

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg; 10 mg; 20 mg; 40 mg; 80 mg (3)

FULL PRESCRIBING INFORMATION

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CONTRAINDICATIONS

- Concomitant administration of strong CYP3A4 inhibitors. (4, 5, 1)
Concomitant administration of gemfibrozil, cyclosporine, or danazol. (4, 5, 1)
Hypersensitivity to any component of this medication (4, 6, 2)
Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels. (4, 5, 2)
Women who are pregnant or may become pregnant. (4, 8, 1)
Nursing mothers. (4, 8, 3)

WARNINGS AND PRECAUTIONS

- Patients should be advised of the increased risk of myopathy including rhabdomyolysis with the 80 mg dose. (5.1)
Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase with higher doses and concomitant use of certain medicines. Predisposing factors include advanced age (≥65), female gender, uncontrolled hypothyroidism, and renal impairment. (4, 5.1, 8.5, 8.6)
Patients should be advised to report promptly any symptoms of myopathy. Simvastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. See Drug Interaction table. (5.1)
Liver enzyme abnormalities: Persistent elevations in hepatic transaminases can occur. Check liver enzyme tests before initiating therapy and as clinically indicated thereafter. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5.0%) are: upper respiratory infection, headache, abdominal pain, constipation, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Zydus Pharmaceuticals USA Inc. at 1-877-993-8779 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.3, 4, 5.1, 7.1, 7.2, 7.3, 12.3)

Table with 2 columns: Interacting Agents and Prescribing Recommendations. Lists drugs like itraconazole, verapamil, amiodarone, and grapefruit juice.

- Other Lipid-lowering Medications: Use with other fibrates products or lipid-modifying doses (≥1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with simvastatin. (5.1, 7.2, 7.4)
Coumarin anticoagulants: Concomitant use with simvastatin prolongs INR. Achieve stable INR prior to starting simvastatin. Monitor INR frequently until stable upon initiation or alteration of simvastatin therapy. (7.6)

USE IN SPECIFIC POPULATIONS

Severe renal impairment: patients should be started at 5 mg/day and be closely monitored. (2.6, 8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2011

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- 1 INDICATIONS AND USAGE
1.1 Reductions in Risk of CHD Mortality and Cardiovascular Events
1.2 Hyperlipidemia
1.3 Adolescent Patients with Heterozygous Familial Hypercholesterolemia (HeFH)

In a clinical trial in 12,064 patients with a history of myocardial infarction were treated with simvastatin (mean follow-up 6.7 years), the incidence of myopathy (defined as unexplained muscle weakness or pain with a serum creatine kinase [CK] > 10 times upper limit of normal [ULN]) in patients on 80 mg/day was approximately 0.9% compared with 0.02% for patients on 20 mg/day. The incidence of rhabdomyolysis (defined as myopathy with a CK > 40 times ULN) in patients on 80 mg/day was approximately 0.4% compared with 0% for patients on 20 mg/day. The incidence of myopathy, including rhabdomyolysis, was highest during the first year and then notably decreased during the subsequent years of treatment. In this trial, patients were carefully monitored and some interacting medicinal products were excluded.

The risk of myopathy, including rhabdomyolysis, is greater in patients on simvastatin 80 mg compared with other statin therapies with similar or greater LDL-C-lowering efficacy and compared with lower doses of simvastatin. Therefore, the 80 mg dose of simvastatin should be used only in patients who have been taking simvastatin 80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity [see DOSAGE AND ADMINISTRATION, Restricted Dosing for 80 mg (2.2)]. If, however, a patient who is currently tolerating the 80 mg dose of simvastatin needs to be initiated on an interacting drug that is contraindicated or is associated with a dose cap for simvastatin, that patient should be switched to an alternative statin with less potential for the drug-drug interaction. Patients should be advised of the increased risk of myopathy, including rhabdomyolysis, and to report promptly any unexplained muscle pain, tenderness or weakness. If symptoms occur, treatment should be discontinued immediately. [See WARNINGS AND PRECAUTIONS (5.2)] All patients starting therapy with simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy, including rhabdomyolysis, and told to report promptly any unexplained muscle pain, tenderness or weakness. Simvastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. In most cases, muscle symptoms and CK increases resolved when treatment was promptly discontinued. Periodic CK determinations may be considered in patients starting therapy with simvastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. Simvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Simvastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.

Drug Interactions
The risk of myopathy and rhabdomyolysis is increased by high levels of statin activity in plasma. Simvastatin is metabolized by the cytochrome P450 isoform 3A4. Certain drugs which inhibit this metabolic pathway can raise the plasma levels of simvastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole and posaconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin. HIV protease inhibitors, the antidepressant nefazodone, or large quantities of grapefruit juice (≥1 quart daily). Combination of these drugs with simvastatin is contraindicated. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin must be suspended during the course of treatment. [See CONTRAINDICATIONS (4) AND DRUG INTERACTIONS (7.1)] In vivo studies have demonstrated a potential for voriconazole to inhibit the metabolism of simvastatin. Adjustment of the simvastatin dose may be needed to reduce the risk of myopathy, including rhabdomyolysis, if voriconazole must be used concomitantly with simvastatin. [See DRUG INTERACTIONS (7.1)] The combined use of simvastatin with gemfibrozil, cyclosporine, or danazol is contraindicated [see CONTRAINDICATIONS (4) AND DRUG INTERACTIONS (7.1) AND (7.2)]. Caution should be used when prescribing other fibrates with simvastatin, as these agents can cause myopathy when given alone and the risk is increased when they are coadministered [see DRUG INTERACTIONS (7.2)]. Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing simvastatin with colchicine. [See DRUG INTERACTIONS (7.7)]. The benefits of the combined use of simvastatin with the following drugs should be carefully weighed against the potential risks of combinations: other lipid-lowering drugs (other fibrates or ≥1 g/day of niacin), amiodarone, verapamil, diltiazem, amlopidine, or ranolazine [see DRUG INTERACTIONS (7.3) and Table 3 in CLINICAL PHARMACOLOGY (12.3)].

Other adverse reactions reported in clinical trials were: diarrhea, rash, dyspepsia, flatulence, and asthenia.
Laboratory Tests
Marked persistent increases of hepatic transaminases have been noted [see WARNINGS AND PRECAUTIONS (5.2)]. Elevated alkaline phosphatase and γ-glutamyl transpeptidase have also been reported. About 5% of patients had elevations of CK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CK [see WARNINGS AND PRECAUTIONS (5.1)].
Adolescent Patients (ages 10 to 17 years)
In a 48-week, controlled study in adolescent boys and girls who were at least 1 year post-menarche, 10 to 17 years of age (43.4% female; 97.7% Caucasians; 1.7% Hispanics; 0.6% Multiracial) with heterozygous familial hypercholesterolemia (n=175), treated with placebo or simvastatin (10 to 40 mg daily), the most common adverse reactions observed in both groups were upper respiratory infection, headache, abdominal pain, and nausea [see USE IN SPECIFIC POPULATIONS (8.4) and Clinical Studies (14.2)].

Post-Marketing Experience
Because the below reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following additional adverse reactions have been identified during postapproval use of simvastatin: pruritus, alopecia, a variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails), dizziness, muscle cramps, myalgia, pancreatitis, paresthesia, peripheral neuropathy, vomiting, anemia, erectile dysfunction, interstitial lung disease, rhabdomyolysis, hepatitis/jaundice, fatal and non-fatal, hepatic failure and depression.
An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome. Arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.
There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, are reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

DRUG INTERACTIONS
Strong CYP3A4 Inhibitors, cyclosporine, or danazol
Strong CYP3A4 Inhibitors
Simvastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of CYP3A4. Simvastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Elevated plasma levels of HMG-CoA reductase inhibitory activity increases the risk of myopathy and rhabdomyolysis, particularly with higher doses of simvastatin [see WARNINGS AND PRECAUTIONS (5.1) and CLINICAL PHARMACOLOGY (12.3)]. Concomitant use of drugs labeled as having a strong inhibitory effect on CYP3A4 is contraindicated [see CONTRAINDICATIONS (4)]. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin must be suspended during the course of treatment. Although not studied clinically, voriconazole has been shown to inhibit voriconazole metabolism in vitro (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentration of simvastatin. It is recommended that dose adjustment of simvastatin be considered during concomitant use of voriconazole and simvastatin to reduce the risk of myopathy, including rhabdomyolysis. [see WARNINGS AND PRECAUTIONS (5.1)]
Cyclosporine or Danazol
The risk of myopathy, including rhabdomyolysis is increased by concomitant administration of cyclosporine or danazol. Therefore, concomitant use of these drugs is contraindicated. [see CONTRAINDICATIONS (4), WARNINGS AND PRECAUTIONS (5.1) AND CLINICAL PHARMACOLOGY (12.3)].
Lipid-Lowering Drugs That Can Cause Myopathy When Given Alone
Gemfibrozil
Concomitant use with simvastatin [see CONTRAINDICATIONS (4) AND WARNINGS AND PRECAUTIONS (5.1)].
Other Fibrates
Caution should be used when prescribing with simvastatin [see WARNINGS AND PRECAUTIONS (5.1)].
Amiodarone, Ranolazine, or Calcium Channel Blockers
The risk of myopathy, including rhabdomyolysis is increased by concomitant administration of amiodarone, ranolazine, or calcium channel blockers such as verapamil, diltiazem, or amlopidine [see DOSAGE AND ADMINISTRATION (2.3) AND WARNINGS AND PRECAUTIONS (5.1), and Table 3 in CLINICAL PHARMACOLOGY (12.3)].
Niacin
Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥1 g/day niacin) of niacin-containing products. In particular, caution should be used when treating Chinese patients with simvastatin doses exceeding 20 mg/day coadministered with lipid-modifying doses of niacin-containing products. Because the risk for myopathy is dose-related, Chinese patients should not receive simvastatin 80 mg coadministered with lipid-modifying doses of niacin-containing products. [see WARNINGS AND PRECAUTIONS (5.1) AND CLINICAL PHARMACOLOGY (12.3)]

Digoxin
In one study, concomitant administration of digoxin with simvastatin resulted in a slight elevation in digoxin concentrations in plasma. Patients taking digoxin should be monitored appropriately when simvastatin is initiated [see CLINICAL PHARMACOLOGY (12.3)].
Coumarin Anticoagulants
In two clinical studies, one in normal volunteers and the other in hypercholesterolemic patients, simvastatin 20 to 40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (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. With other statins, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, 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 or discontinued, 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.

Colchicine
Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing simvastatin with colchicine.
Caution should be used when prescribing with simvastatin [see WARNINGS AND PRECAUTIONS (5.1)].

Table with 2 columns: Interacting Agents and Prescribing Recommendations. Lists drugs like itraconazole, verapamil, amiodarone, and grapefruit juice.

Liver Dysfunction
Persistent increases (to more than 3X the ULN) in serum transaminases have occurred in approximately 1% of patients who received simvastatin in clinical studies. When drug treatment 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.
In the Scandinavian Simvastatin Survival Study (4S) [see Clinical Studies (14.1)], the number of patients with more than one transaminase elevation to >3X ULN, over the course of the study, was not significantly different between the simvastatin and placebo groups (14 [0.7%] vs. 12 [0.6%]). Elevated transaminases resulted in the discontinuation of 8 patients from therapy in the simvastatin group (n=2,221) and 5 in the placebo group (n=2,223). Of the 1,986 simvastatin-treated patients in 4S with normal liver function tests (LFTs) at baseline, 8 (0.4%) developed consecutive LFT elevations to >3X ULN and/or were discontinued due to transaminase elevations during the 5.4 years (median follow-up) of the study. Among these 8 patients, 5 initially developed these abnormalities within the first year. All of the patients in this study received a starting dose of 20 mg of simvastatin; 37% were titrated to 40 mg. Then one transaminase elevation to >3X ULN, over the course of the study, was not significantly different between the simvastatin and placebo groups (14 [0.7%] vs. 12 [0.6%]). Elevated transaminases resulted in the discontinuation of 8 patients from therapy in the simvastatin group (n=2,221) and 5 in the placebo group (n=2,223). Of the 1,986 simvastatin-treated patients in 4S with normal liver function tests (LFTs) at baseline, 8 (0.4%) developed consecutive LFT elevations to >3X ULN and/or were discontinued due to transaminase elevations during the 5.4 years (median follow-up) of the study. Among these 8 patients, 5 initially developed these abnormalities within the first year. 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 1,105 patients, the 12-month incidence of persistent hepatic transaminase elevation without regard to drug relationship was 0.9% and 2.1% at the 40- and 80-mg dose, respectively. No patients developed persistent liver function abnormalities following the initial 6 months of treatment at a given dose.
It is recommended that liver function tests be performed before the initiation of treatment, and thereafter when clinically indicated. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including simvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during ALT treatment with simvastatin, promptly interrupt therapy. If an alternate etiology is not found, discontinue simvastatin. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy [see WARNINGS AND PRECAUTIONS (5.1)]. The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of simvastatin.

As with other lipid-lowering agents, moderate (less than 3X ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and did not require interruption of treatment.
Endocrine Function
Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including simvastatin.

ADVERSE REACTIONS
Clinical Trials Experience
Concomitant administration was conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. In the pre-marketing controlled clinical studies and their open extensions (2,423 patients with median duration of follow-up of approximately 18 months), 1.4% of patients were discontinued due to adverse reactions. The most common adverse reactions that led to discontinuation were: upper respiratory infection (0.5%), myalgia (0.5%), myasthenia (0.1%), and constipation (0.1%). The most commonly reported adverse reactions (incidence ≥5%) in simvastatin controlled clinical trials were: upper respiratory infections (9.0%), headache (7.4%), abdominal pain (7.3%), constipation (6.6%), and nausea (5.4%).

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Scandinavian Simvastatin Survival Study
In 4S involving 4,444 patients (age range 35 to 64 years, 19% women, 100% Caucasians) treated with 20 to 40 mg/day of simvastatin (n=2,221) or placebo (n=2,223) over a median of 5.4 years, adverse reactions reported in 22% of patients and at a rate greater than placebo are shown in Table 2.

Table 2 Adverse Reactions Reported Regardless of Causality by ≥2% of Patients Treated with Simvastatin and Greater than Placebo in 4S

Table with 3 columns: Adverse Reaction, Simvastatin (N=2,221) %, Placebo (N=2,223) %. Lists reactions like Body as a Whole, Cardiovascular System Disorders, Digestive System Disorders, etc.

Heart Protection Study (HPS), involving 20,536 patients (age range 40 to 80 years, 25% women, 97% Caucasians, 3% other races) treated with simvastatin 40 mg/day (n=10,269) or placebo (n=10,267) over a mean of 5 years, only serious adverse reactions and discontinuations due to any adverse reactions were recorded. Discontinuation rates due to adverse reactions were 4.8% in patients treated with simvastatin compared with 5.1% in patients treated with placebo. The incidence of myopathy/rhabdomyolysis was <0.1% in patients treated with simvastatin.

Other Clinical Studies
In a clinical trial in 12,064 patients with a history of myocardial infarction were treated with simvastatin (mean follow-up 6.7 years), the incidence of myopathy (defined as unexplained muscle weakness or pain with a serum creatine kinase [CK] > 10 times upper limit of normal [ULN]) in patients on 80 mg/day was approximately 0.9% compared with 0.02% for patients on 20 mg/day. The incidence of rhabdomyolysis (defined as myopathy with a CK > 40 times ULN) in patients on 80 mg/day was approximately 0.4% compared with 0% for patients on 20 mg/day. The incidence of myopathy, including rhabdomyolysis, was highest during the first year and then notably decreased during the subsequent years of treatment. In this trial, patients were carefully monitored and some interacting medicinal products were excluded.

Other adverse reactions reported in clinical trials were: diarrhea, rash, dyspepsia, flatulence, and asthenia.
Laboratory Tests
Marked persistent increases of hepatic transaminases have been noted [see WARNINGS AND PRECAUTIONS (5.2)]. Elevated alkaline phosphatase and γ-glutamyl transpeptidase have also been reported. About 5% of patients had elevations of CK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CK [see WARNINGS AND PRECAUTIONS (5.1)].

Adolescent Patients (ages 10 to 17 years)
In a 48-week, controlled study in adolescent boys and girls who were at least 1 year post-menarche, 10 to 17 years of age (43.4% female; 97.7% Caucasians; 1.7% Hispanics; 0.6% Multiracial) with heterozygous familial hypercholesterolemia (n=175), treated with placebo or simvastatin (10 to 40 mg daily), the most common adverse reactions observed in both groups were upper respiratory infection, headache, abdominal pain, and nausea [see USE IN SPECIFIC POPULATIONS (8.4) and Clinical Studies (14.2)].

Post-Marketing Experience
Because the below reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following additional adverse reactions have been identified during postapproval use of simvastatin: pruritus, alopecia, a variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails), dizziness, muscle cramps, myalgia, pancreatitis, paresthesia, peripheral neuropathy, vomiting, anemia, erectile dysfunction, interstitial lung disease, rhabdomyolysis, hepatitis/jaundice, fatal and non-fatal, hepatic failure and depression.

An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome. Arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

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

DRUG INTERACTIONS
Strong CYP3A4 Inhibitors, cyclosporine, or danazol
Strong CYP3A4 Inhibitors
Simvastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of CYP3A4. Simvastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Elevated plasma levels of HMG-CoA reductase inhibitory activity increases the risk of myopathy and rhabdomyolysis, particularly with higher doses of simvastatin [see WARNINGS AND PRECAUTIONS (5.1) and CLINICAL PHARMACOLOGY (12.3)]. Concomitant use of drugs labeled as having a strong inhibitory effect on CYP3A4 is contraindicated [see CONTRAINDICATIONS (4)]. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin must be suspended during the course of treatment. Although not studied clinically, voriconazole has been shown to inhibit voriconazole metabolism in vitro (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentration of simvastatin. It is recommended that dose adjustment of simvastatin be considered during concomitant use of voriconazole and simvastatin to reduce the risk of myopathy, including rhabdomyolysis. [see WARNINGS AND PRECAUTIONS (5.1)]

Cyclosporine or Danazol
The risk of myopathy, including rhabdomyolysis is increased by concomitant administration of cyclosporine or danazol. Therefore, concomitant use of these drugs is contraindicated. [see CONTRAINDICATIONS (4), WARNINGS AND PRECAUTIONS (5.1) AND CLINICAL PHARMACOLOGY (12.3)].

Lipid-Lowering Drugs That Can Cause Myopathy When Given Alone
Gemfibrozil
Concomitant use with simvastatin [see CONTRAINDICATIONS (4) AND WARNINGS AND PRECAUTIONS (5.1)].
Other Fibrates
Caution should be used when prescribing with simvastatin [see WARNINGS AND PRECAUTIONS (5.1)].

Amiodarone, Ranolazine, or Calcium Channel Blockers
The risk of myopathy, including rhabdomyolysis is increased by concomitant administration of amiodarone, ranolazine, or calcium channel blockers such as verapamil, diltiazem, or amlopidine [see DOSAGE AND ADMINISTRATION (2.3) AND WARNINGS AND PRECAUTIONS (5.1), and Table 3 in CLINICAL PHARMACOLOGY (12.3)].

Niacin
Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥1 g/day niacin) of niacin-containing products. In particular, caution should be used when treating Chinese patients with simvastatin doses exceeding 20 mg/day coadministered with lipid-modifying doses of niacin-containing products. Because the risk for myopathy is dose-related, Chinese patients should not receive simvastatin 80 mg coadministered with lipid-modifying doses of niacin-containing products. [see WARNINGS AND PRECAUTIONS (5.1) AND CLINICAL PHARMACOLOGY (12.3)]

Digoxin
In one study, concomitant administration of digoxin with simvastatin resulted in a slight elevation in digoxin concentrations in plasma. Patients taking digoxin should be monitored appropriately when simvastatin is initiated [see CLINICAL PHARMACOLOGY (12.3)].

Coumarin Anticoagulants
In two clinical studies, one in normal volunteers and the other in hypercholesterolemic patients, simvastatin 20 to 40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (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. With other statins, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, 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 or discontinued, 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.

Colchicine
Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing simvastatin with colchicine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X (see CONTRAINDICATIONS (4)).
Simvastatin is contraindicated in women who are or may become pregnant. Lipid lowering drugs offer no benefit during pregnancy, because cholesterol and cholesterol derivatives are needed for normal fetal development. Atherosclerosis is a chronic process, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholesterolemia therapy. There are no adequate and well-controlled studies of use with simvastatin during pregnancy; however, there are rare reports of congenital anomalies in infants exposed to statins in utero. Animal reproduction studies of simvastatin in rats and rabbits showed no evidence of teratogenicity. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Because statins decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, simvastatin may cause fetal harm when administered to a pregnant woman. If simvastatin is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

There are rare reports of congenital anomalies following intrauterine exposure to statins. In a review of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or another structurally related statin, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed those expected in the general population. However, the study was only able to exclude a 3- to 4-fold increased risk of congenital anomalies over the background rate. In 89% of these cases, drug treatment was initiated prior to pregnancy and was discontinued during the first trimester when pregnancy was identified.

Manson, J.M., Freysing, C., Ducrocq, M.B., Thompson, W.P. Postmarketing Surveillance of Lovastatin and Simvastatin Exposure During Pregnancy. *Reproductive Toxicology*, 10(6):439-446, 1996.

Simvastatin was not teratogenic in rats or rabbits at doses (25, 100 mg/kg/day, respectively) that resulted in 3 times the human exposure based on mg/m² surface area. However, in studies with another structurally-related statin, skeletal malformations were observed in rats and mice.

Women of childbearing potential, who require treatment with simvastatin for a lipid disorder, should be advised to use effective contraception. For women trying to conceive, discontinuation of simvastatin should be considered. If pregnancy occurs, simvastatin should be immediately discontinued.

8.2 Nursing Mothers

It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants. A decision should be made to discontinue nursing or discontinue drug, taking into account the importance of the drug to the mother (see CONTRAINDICATIONS (4)).

8.3 Pediatric Use

Safety and effectiveness of simvastatin in patients 10 to 17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent children in girls who were at least 1 year post-menarche. Patients treated with simvastatin had an adverse reaction profile 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 significant effect on growth or sexual maturation in the adolescent boys or girls, or on menstrual cycle length in girls (see **DOSE AND ADMINISTRATION (2.5), ADVERSE REACTIONS (6.1), Clinical Studies (14.2)**). Adolescent patients should be counseled on appropriate contraceptive methods while on simvastatin therapy (see **CONTRAINDICATIONS (4)** and **USE IN SPECIFIC POPULATIONS (8.1)**). Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

8.4 Geriatric Use

Of the 4,243 patients who received simvastatin in Phase III clinical studies and the 10,269 patients in the Heart Protection Study who received simvastatin, 363 (15%) and 5,366 (52%), respectively, were ≥65 years old. In HPS, 615 (6%) were ≥75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Since advanced age (≥65 years) is a predisposing factor for myopathy, simvastatin should be prescribed with caution in the elderly (see **CLINICAL PHARMACOLOGY (12.3)**). A pharmacokinetic study with simvastatin showed the mean plasma level of statin activity to be approximately 45% higher in elderly patients between 70 to 78 years of age compared with patients between 18 to 30 years of age. In HPS, 1,021 (23%) of 4,444 patients were 65 or older. Lipid-lowering efficacy was at least as great in elderly patients compared with younger patients, and simvastatin significantly reduced total mortality and CHD mortality in elderly patients with a history of CHD. In HPS, 52% of patients were elderly (4,891 patients 65 to 69 years and 5,806 patients 70 years or older). The relative risk reductions of CHD death, non-fatal MI, coronary and non-coronary revascularization procedures, and stroke were similar in older and younger patients (see **Clinical Studies (14.1)**). In HPS, among 32,145 patients entering the active run-in period, there were 2 cases of myopathy/rhabdomyolysis; these patients were aged 67 and 73. Of the 7 cases of myopathy/rhabdomyolysis among 10,269 patients allocated to simvastatin, 4 were aged 65 or more (at baseline), of whom one was over 75. There were no overall differences in safety between older and younger patients in either HPS.

Because advanced age (≥ 65 years) is a predisposing factor for myopathy, including rhabdomyolysis, simvastatin should be prescribed with caution in the elderly. In a clinical trial of patients treated with simvastatin 80 mg/day, patients ≥ 65 years of age had an increased risk of myopathy, including rhabdomyolysis, compared to patients < 65 years of age. (see **WARNINGS AND PRECAUTIONS (5.1) AND CLINICAL PHARMACOLOGY (12.3)**).

8.5 Renal Impairment

Caution should be exercised when simvastatin is administered to patients with severe renal impairment (see **DOSE AND ADMINISTRATION (2.6)**).

8.6 Hepatic Impairment

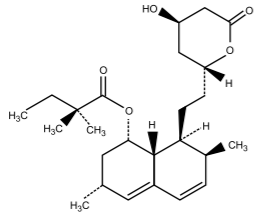
Simvastatin is contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels (see **CONTRAINDICATIONS (4)** and **WARNINGS AND PRECAUTIONS (5.1)**).

10 OVERDOSE

Significant lethality was observed in mice after a single oral dose of 9 g/m². No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 mg/m², respectively. No specific diagnostic signs were observed in rodents. At these doses the only signs seen in dogs were emesis and mucoid stools. A few cases of overdose with simvastatin have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae. Supportive measures should be taken in the event of an overdose. The dialyzability of simvastatin and its metabolites in man is not known at present.

11 DESCRIPTION

Simvastatin is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is an 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 rate-limiting step in cholesterol biosynthesis. Simvastatin is butyric 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-(1,2,3a,7b,8b)(2S',4S')-8aH]. The molecular formula of simvastatin is C₂₈H₄₄O₇ and its molecular weight is 418.57. Its structural formula is:



Simvastatin USP is a white to off-white powder that is practically insoluble in water; freely soluble in chloroform, in methanol and in alcohol; sparingly soluble in propylene glycol; very slightly soluble in hexane. Each simvastatin tablet intended for oral administration contains 5 mg or 10 mg or 20 mg or 40 mg or 80 mg of simvastatin. In addition, each tablet contains the following inactive ingredients: ascorbic acid, citric acid anhydrous, hydroxypropyl cellulose, hydroxypropyl methylcellulose (hypromellose), lactose anhydrous, magnesium stearate, pregelatinized starch, talc and titanium dioxide. Additionally each 10 mg tablet contains iron oxide red and iron oxide yellow, 20 mg tablet contains iron oxide black, iron oxide red and iron oxide yellow and 40 mg tablet contains iron oxide red. Butylated hydroxyanisole is added as a preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Simvastatin is a prodrug and is hydrolyzed to its active β-hydroxyacid form, simvastatin acid, after administration. Simvastatin is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early and rate limiting step in the biosynthetic pathway for cholesterol. In addition, simvastatin reduces VLDL and TG and increases HDL-C.

12.2 Pharmacodynamics

Epidemiological studies have demonstrated that elevated levels of total-C, LDL-C, as well as decreased levels of HDL-C are associated with the development of atherosclerosis and increased cardiovascular risk. Lowering LDL-C decreases this risk. However, the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

12.3 Pharmacokinetics

Simvastatin is a lactone that is readily hydrolyzed in vivo to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the β-hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin. Following an oral dose of ¹⁴C-labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces. Plasma concentrations of total radioactivity (simvastatin plus C-metabolites) peaked at 4 hours and declined rapidly to about 10% of peak by 12 hours postdose. Since simvastatin undergoes extensive first-pass extraction in the liver, the availability of the drug to the general circulation is low (<5%). Both simvastatin and its β-hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins. Rat studies indicate that when radiolabeled simvastatin was administered, simvastatin-derived radioactivity crossed the blood-brain barrier. The major active metabolites of simvastatin present in human plasma are the β-hydroxyacid of simvastatin and its 6'-hydroxy-, 6'-hydroxymethyl-, and 6'-oxomethylene derivatives. Peak plasma concentrations of both active and total inhibitors were attained within 1.3 to 2.4 hours postdose. While the recommended therapeutic dose range is 5 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 an American Heart Association recommended low-fat meal.

In a study including 16 elderly patients between 70 and 78 years of age who received simvastatin 40 mg/day, the mean plasma level of HMG-CoA reductase inhibitory activity was increased approximately 45% compared with 18 patients between 18 to 30 years of age. Clinical study experience in the elderly (n=1522), suggests that there were no overall differences in safety between elderly and younger patients (see **USE IN SPECIFIC POPULATIONS (8.5)**). Kinetic studies with another statin, having a similar principal route of elimination, have suggested that for a given dose level higher plasma concentrations are achieved in patients with decreased renal insufficiency (as measured by creatinine clearance). Although the mechanism is not fully understood, cyclosporine has been shown to increase the AUC of statins. The increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Inhibitors of CYP3A4 can raise plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy (see **WARNINGS AND PRECAUTIONS (5.1) AND DRUG INTERACTIONS (7.1)**).

Effect of Coadministered Drugs or Grapefruit Juice on Simvastatin Systemic Exposure

Coadministered Drug or Grapefruit Juice	Dosing of Coadministered Drug or Grapefruit Juice	Simvastatin	Geometric Mean Ratio (Ratio) without/with Coadministered Drug		
			No Effect = 1.00	AUC	C _{max}
Telitromycin ¹	200 mg QD for 4 days	80 mg	simvastatin acid ²	12	15
			simvastatin	8.9	5.3
Nefinavir ¹	1250 mg BID for 14 days	20 mg QD for 28 days	simvastatin acid ²	6	6.2
			simvastatin	13.1	13.1
Itraconazole ¹	200 mg QD for 4 days	80 mg	simvastatin acid ²	7.3	9.2
			simvastatin	10.3	9.4
Posaconazole ¹	100 mg (oral suspension) QD for 13 days	40 mg	Simvastatin acid ²	8.5	9.5
			simvastatin	10.6	11.4
Gemfibrozil ¹	600 mg BID for 3 days	40 mg	Simvastatin acid ²	2.85	2.18
			simvastatin	1.35	0.91

Avoid ≥ 1 quart of grapefruit juice with simvastatin (see **WARNINGS AND PRECAUTIONS (5.1)**)

Drug	Dose	Simvastatin	Ratio
Grapefruit Juice ¹ (high dose)	200 mL of double strength TID	60 mg single dose	simvastatin acid 7
Grapefruit Juice ¹ (low dose)	8 oz (about 237 mL) of single-strength ¹	20 mg single dose	simvastatin acid 1.6
		Simvastatin	1.9

Avoid taking with ≥ 10 mg simvastatin, based on clinical and/or post-marketing experience (see **WARNINGS AND PRECAUTIONS (5.1)**)

Drug	Dose	Simvastatin	Ratio
Verapamil SR	240 mg QD Days 1-7 then 240 mg BID on Days 8-10	80 mg on Day 10	simvastatin acid 2.3, 2.4 simvastatin 2.5, 2.1
Diltiazem	120 mg BID for 14 days	80 mg on Day 10	simvastatin 3.69, 2.69 simvastatin 3.10, 2.88
Diltiazem	120 mg BID for 14 days	20 mg on Day 14	simvastatin 4.6, 3.6

Avoid taking with ≥ 20 mg simvastatin, based on clinical and/or post-marketing experience (see **WARNINGS AND PRECAUTIONS (5.1)**)

Drug	Dose	Simvastatin	Ratio
Amiodarone	400 mg QD for 3 days	40 mg on Day 3	simvastatin acid 1.75, 1.72 simvastatin 1.78, 1.79
Amlodipine	10 mg QD x 10 days	80 mg on Day 10	simvastatin acid 1.56, 1.56 simvastatin 1.77, 1.47
Ranolazine SR	1000 mg BID for 7 days	80 mg on Day 1 and Day 6-9	simvastatin acid 2.26, 2.28 simvastatin 1.86, 1.75

Not dosing adjustments required for the following:

Drug	Dose	Simvastatin	Ratio
Fenofibrate	160 mg QD x 14 days	80 mg QD on Days 8 to 14	simvastatin acid 0.64, 0.89
Niacin Extended-Release ¹	2 g single dose	20 mg single dose	simvastatin 0.89, 0.83 simvastatin acid 1.6, 1.84
Diltiazem	120 mg BID for 10 Days	80 mg on Day 10	simvastatin acid 1.4, 1.08 simvastatin 2.69, 2.69
Propranolol	80 mg single dose	80 mg single dose	simvastatin 3.10, 2.88 total inhibitor 0.79, 1.08 active inhibitor 0.79, 1.08

Mean Response in Patients with Primary Hyperlipidemia and Combined (Mixed) Hyperlipidemia (Mean Percent Change from Baseline After 6 to 24 Weeks)

TREATMENT	N	TOTAL-C	LDL-C	HDL-C	TG ¹
Lower Dose Comparison Study ² (Mean % Change at Week 6)					
Simvastatin 10 mg q.p.m.	109	-19	-26	10	-12
Simvastatin 20 mg q.p.m.	109	-23	-30	12	-15
Upper Dose Comparison Study ³ (Mean % Change Averaged at Weeks 18 and 24)					
Simvastatin 40 mg q.p.m. ⁴	433	-31	-41	9	-18
Simvastatin 80 mg q.p.m. ⁴	664	-36	-47	8	-24
Multi-Center Combined Hyperlipidemia Study ⁵ (Mean % Change at Week 6)					
Placebo	125	1	2	3	-4
Simvastatin 40 mg q.p.m.	123	-25	-29	13	-28
Simvastatin 80 mg q.p.m.	124	-31	-36	16	-33

¹ median percent change

² mean baseline LDL-C 244 mg/dL and median baseline TG 168 mg/dL

³ mean baseline LDL-C 188 mg/dL and median baseline TG 128 mg/dL

⁴ mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL

⁵ mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL

⁶ mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL

⁷ mean baseline LDL-C 156 mg/dL and median baseline TG 391 mg/dL

⁸ Hypertriglyceridemia (Fredrickson type IV)

The results of a subgroup analysis in 74 patients with type IV hyperlipidemia from a 130-patient, double-blind, placebo-controlled, 3-period crossover study are presented in Table 7.

⁹ mean baseline LDL-C 244 mg/dL and median baseline TG 168 mg/dL

¹⁰ mean baseline LDL-C 188 mg/dL and median baseline TG 128 mg/dL

¹¹ mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL

¹² mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL

¹³ mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL

¹⁴ mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL

¹⁵ mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL

¹⁶ mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL

¹⁷ mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL

¹⁸ mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL

¹⁹ mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL

²⁰ mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL

²¹ mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL

²² mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL

²³ mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL

²⁴ mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL

²⁵ mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL

niacin) of niacin-containing products, and the risk is dose-related. Chinese patients should not receive simvastatin 80 mg coadministered with lipid-modifying doses of niacin-containing products (see **WARNINGS AND PRECAUTIONS (5.1) AND Drug Interactions (7.4)**).

In a study of healthy volunteers, simvastatin at the 80-mg dose had no effect on the metabolism of the probe cytochrome P450 isoform 3A4 (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. Coadministration of simvastatin (40 mg QD for 10 days) resulted in an increase in the maximum mean levels of cardioactive digoxin (given as a single dose on Day 10) by approximately 0.3 mg/mL.

13.1 NONCLINICAL TOXICOLOGY

13.1.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8 times higher than the mean human plasma drug level, respectively (as total inhibitory activity based on AUC) after an 80-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90%. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day. In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed (mean plasma drug levels were 1 times higher than humans given 80 mg simvastatin as measured by AUC).

In a 2-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC). A second 2-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other statins. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males and 22 and 25 times (females) the mean human plasma drug level after an 80 milligram daily dose.

No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of mutagenicity was observed in *in vitro* alkaline comet assay, *in vitro* sister chromatid exchanges, 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.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level based on AUC) in patients treated with simvastatin. This effect was observed in a study of the effect of fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day, which produces exposure levels 22 times higher than those in humans taking 80 mg/day based on surface area, 100% seminiferous tubule degeneration (necrosis and loss of spermatogenic cells) was observed. In addition, there was reduced testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day (approximately 2 times the human exposure, based on AUC, at 80 mg/day). The clinical significance of these findings is unclear.

13.1.2 Toxicology and/or Pharmacology

CNS Toxicity

Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the mean plasma drug level in humans taking 80 mg/day. A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean plasma drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels were seen in dogs treated with simvastatin at a dose of 300 mg/kg/day. A dose that produced mean plasma drug levels that were about 14 times higher than the mean plasma drug levels in humans taking 80 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

There were catarracts in female rats after two months of treatment with 50 and 100 mg/kg/day (22 and 25 times the human AUC at 80 mg/kg/day) and in dogs after three months at 80 mg/kg/day (19 times) and at two years at 50 mg/kg/day (5 times).

14 CLINICAL STUDIES

14.1 Clinical Studies in Adults

Reductions in Risk of CHD Mortality and Cardiovascular Events

In AS, the effect of simvastatin on total mortality was assessed in 4,444 patients with CHD and baseline total cholesterol 212 to 309 mg/dL (5.5 to 8.0 mmol/L). In this multicenter, randomized, double-blind, placebo-controlled study, patients were treated with standard care, including diet, and either simvastatin 20 to 40 mg/day (n=2,221) or placebo (n=2,223) for a median duration of 5.4 years over the course of the study; treatment with simvastatin led to mean reductions in risk of LDL-C and TG of 25%, 35%, and 10%, respectively, and a mean increase in HDL-C of 6%. Simvastatin significantly reduced the risk of mortality by 30% (p<0.0003, 182 deaths in the simvastatin group vs 256 deaths in the placebo group). The risk of CHD mortality was significantly reduced by 42% (p<0.0001, 111 vs 189 deaths). There was no statistically significant difference between groups in non-cardiovascular mortality. Simvastatin significantly reduced the risk of major coronary events (CHD mortality plus hospital-verified and silent nonfatal myocardial infarction [MI]) by 34% (p<0.0001, 431 vs 622 patients with one or more events). The risk of having a hospital-verified non-fatal MI was reduced by 37%. Simvastatin significantly reduced the risk of undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37% (p<0.0001, 252 vs 383 patients). Simvastatin significantly reduced the risk of fatal plus non-fatal cerebrovascular events (combined stroke and transient ischemic attacks) by 28% (p<0.033, 75 vs 102 patients). Simvastatin reduced the risk of major coronary events to a similar extent across the range of baseline total and LDL cholesterol levels. Because there were only 53 female deaths, the effect of simvastatin on mortality in women could not be adequately assessed. However, simvastatin significantly lessened the risk of having major coronary events and major coronary events with one or more events. The randomization was stratified by angina alone (21% of each treatment group) or a previous MI. Because there were only 57 deaths among the patients with angina alone at baseline, the effect of simvastatin on mortality in this subgroup could not be adequately assessed. However, trends in reduced coronary mortality, major coronary events, and major coronary events with one or more events were consistent between this group and the total study cohort. Additionally, simvastatin resulted in similar decreases in relative risk for total mortality, CHD mortality, and major coronary events in elderly patients (≥65 years), compared with younger patients.

The Heart Protection Study (HPS) was a large, multi-center, placebo-controlled, double-blind study with a mean duration of 5 years conducted in 20,538 patients aged 40 to 70 years with CHD and baseline total cholesterol 160 to 260 mg/dL. Patients were allocated to treatment using a covariate adaptive method¹ which took into account the distribution of 10 important baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients had a mean age of 64 years (range 40 to 80 years), were 87% Caucasian and were at high risk of developing a major coronary event because of existing CHD (65%), diabetes (Type 2, 26%), history of stroke (21%), history of stroke with MI, baseline concomitant cardiovascular medications (i.e., aspirin, beta blockers, or calcium channel blockers), smoking status, alcohol intake, or obesity. Diabetics showed risk reductions for MCE and MVE due to simvastatin treatment regardless of baseline HbA1c levels or obesity with the greatest effects seen for diabetics without CHD.

The HPS results showed that simvastatin 40 mg/day significantly reduced: total and CHD mortality; nonfatal MI, stroke, and revascularization procedures (coronary and non-coronary) (see Table 4).

Summary of Heart Protection Study Results

Endpoint	Simvastatin (N=10,269) n (%)	Placebo (N=10,267) n (%)	Risk Reduction (%) (95% CI)	p-Value
Primary				
Mortality	1,328 (12.9)	1,507 (14.7)	13 (8 to 16)	p<0.0003
CHD mortality	587 (5.7)	707 (6.9)	18 (8 to 26)	p<0.0005
Secondary				
Non-fatal MI	357 (3.5			