PHYSICIANS CIRCULAR

Tablets
ZOCOR®†
(simvastatin, USP)

ZOCOR (simvastatin, USP) is a lipid-lowering agent derived synthetically from a fermentation product of *Aspergillus terreus*.

After oral ingestion, ZOCOR, an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is a principal metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes an early and rate-limiting step in the biosynthesis of cholesterol. Clinical studies show ZOCOR to be highly effective in reducing total plasma cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and very-low-density lipoprotein cholesterol (VLDL-C) concentrations, and increasing high-density lipoprotein cholesterol (HDL-C) in heterozygous familial and non-familial forms of hypercholesterolemia, and in mixed hyperlipidemia when elevated cholesterol was cause for concern and diet alone has been insufficient. Marked responses are seen within 2 weeks, and maximum therapeutic responses occur within 4-6 weeks. The response is maintained during continuation of therapy. When therapy with ZOCOR is stopped, cholesterol and lipids return to pretreatment levels.

The active form of simvastatin is a specific inhibitor of HMG-CoA reductase, the enzyme which catalyzes the conversion of HMG-CoA to mevalonate. Because the conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway of cholesterol, therapy with ZOCOR would not be expected to cause an accumulation of potentially toxic sterols. In addition, HMG-CoA is also metabolized readily back to acetyl-CoA, which participates in many biosynthetic processes in the body.

In animal studies, after oral dosing, simvastatin had high selectivity for the liver, where it achieved substantially higher concentrations than in non-target tissues. Simvastatin undergoes extensive first-pass extraction in the liver, the primary site of action, with subsequent excretion of drug in the bile. Systemic exposure of the active form of simvastatin in man has been found to be less than 5% of the oral dose. Of this, 95% is bound to human plasma proteins.

In the Scandinavian Simvastatin Survival Study (4S), the effect on total mortality of therapy with ZOCOR for a median of 5.4 years was assessed in 4,444 patients with coronary heart disease (CHD) and baseline total-C 212-309 mg/dL (5.5-8.0 mmol/L). In this multicenter, randomized, double-blind, placebo-controlled study, ZOCOR reduced the risk of death by 30%, of CHD death by 42%, and of having a hospital-verified nonfatal myocardial infarction by 37%. ZOCOR reduced the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37%. In patients with diabetes mellitus the risk of a major coronary event was reduced by 55%. Furthermore, ZOCOR significantly reduced the risk of fatal plus nonfatal cerebrovascular events (stroke and transient ischemic attacks) by 28%.

In the Heart Protection Study (HPS), the effects of therapy with ZOCOR for a mean duration of 5 years were assessed in 20,536 patients, with or without hyperlipidemia, who were at high risk of coronary heart disease (CHD) events because of diabetes, history of stroke or other cerebrovascular disease, peripheral vessel disease, or CHD. At baseline, 33% had LDL levels below 116 mg/dL; 25% had levels between 116 mg/dL and 135 mg/dL; and 42% had levels greater than 135 mg/dL.

In this multicenter, randomized, double-blind, placebo-controlled study, ZOCOR 40 mg/day compared with placebo reduced the risk of total mortality by 13%, due to a reduction in CHD deaths (18%). ZOCOR also decreased the risk of major coronary events (a composite endpoint comprising non-fatal MI or CHD deaths) by 27%. ZOCOR reduced the need for undergoing coronary revascularization procedures (including coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) and peripheral and other non-coronary revascularization procedures by 30% and 16%, respectively. ZOCOR reduced the risk of stroke by 25%. Furthermore, ZOCOR reduced the risk of

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hospitalization for angina pectoris by 17%. The risks of major coronary events and major vascular events (a composite endpoint comprising major coronary events, stroke, or revascularization procedures) were reduced by about 25% in patients with or without CHD, including diabetics and patients with peripheral or cerebrovascular disease. In addition, within the subgroup of patients with diabetes, ZOCOR reduced the risk of developing macrovascular complications, including peripheral revascularization procedures (surgery or angioplasty), lower limb amputations, or leg ulcers by 21%. The risk reductions produced by ZOCOR in both major vascular events and major coronary events were evident and consistent regardless of patient age, gender, baseline LDL-C, HDL-C, TG, apolipoprotein A-I, or apolipoprotein B level, presence or absence of hypertension, creatinine levels up to the entry limit of 2.3 mg/dL, presence or absence of baseline cardiovascular medications (i.e., aspirin, beta blockers, angiotensin converting enzyme (ACE) inhibitors, or calcium channel blockers), smoking status, alcohol intake, or obesity. By 5 years, 32% of patients in the placebo group were taking a statin (outside of the study protocol), so that the observed risk reductions underestimate the real effect of simvastatin.

In a multicenter, placebo-controlled clinical study in 404 patients using quantitative coronary angiography, ZOCOR slowed the progression of coronary atherosclerosis and reduced the development of both new lesions and new total occlusions, whereas coronary atherosclerotic lesions steadily worsened over four years in patients receiving standard care.

Subgroup analyses from 2 studies including a total of 147 patients with hypertriglyceridemia (Fredrickson type IV hyperlipidemia) demonstrated that ZOCOR at doses of 20 to 80 mg/day reduced TG 21 to 39% (placebo: 11 to 13%), LDL-C 23 to 35% (placebo: +1 to +3%), non-HDL-C 26 to 43% (placebo: 1 to 3%), and raised HDL-C by 9 to 14% (placebo: 3%).

In another subgroup analysis of 7 patients with dysbetalipoproteinemia (Fredrickson type III hyperlipidemia), ZOCOR at a dosage of 80 mg/day reduced LDL-C including intermediate-density lipoproteins (IDL) by 51% (placebo: 8%) and VLDL-C + IDL by 60% (placebo: 4%).

INDICATIONS

PATIENTS AT HIGH RISK OF CORONARY HEART DISEASE (CHD) OR WITH EXISTING CHD

In patients at high risk of CHD (with or without hyperlipidemia), i.e., patients with diabetes, history of stroke or other cerebrovascular disease, peripheral vessel disease, or with existing CHD, ZOCOR is indicated to:

- Reduce the risk of total mortality by reducing CHD deaths;
- Reduce the risk of major vascular events (a composite of non-fatal myocardial infarction, CHD death, stroke, or revascularization procedures);
- Reduce the risk of major coronary events (a composite of non-fatal myocardial infarction or CHD deaths);
- Reduce the risk of stroke;
- Reduce the need for coronary revascularization procedures (including coronary artery bypass grafting and percutaneous transluminal coronary angioplasty);
- Reduce the need for peripheral and other non-coronary revascularization procedures;
- Reduce the risk of hospitalization for angina pectoris.

In patients with diabetes, ZOCOR reduces the risk of developing peripheral macrovascular complications (a composite of peripheral revascularization procedures, lower limb amputations, or leg ulcers).

In hypercholesterolemic patients with coronary heart disease, ZOCOR slows the progression of coronary atherosclerosis, including reducing the development of new lesions and new total occlusions.

PATIENTS WITH HYPERLIPIDEMIA

- ZOCOR is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, TG, and apolipoprotein B (apo B), and to increase HDL-C in patients with primary hypercholesterolemia including heterozygous familial hypercholesterolemia (Fredrickson type IIa), or combined (mixed) hyperlipidemia (Fredrickson type IIb), when response to diet and other nonpharmacological measures is inadequate. ZOCOR, therefore, lowers LDL-C/HDL-C and total-C/HDL-C ratios.
- ZOCOR is indicated for the treatment of patients with hypertriglyceridemia (Fredrickson type IV hyperlipidemia).
- ZOCOR is indicated for the treatment of patients with primary dysbetalipoproteinemia (Fredrickson type III hyperlipidemia).
- ZOCOR is also indicated as an adjunct to diet and other non-dietary measures for the treatment of patients with homozygous familial hypercholesterolemia to reduce elevated total-C, LDL-C and apo B.

PEDIATRIC PATIENTS WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

ZOCOR 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).

DOSAGE AND ADMINISTRATION

The dosage range for ZOCOR is 5-80 mg/day, given as a single dose in the evening. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80 mg/day given as a single dose in the evening. The 80-mg dose of ZOCOR should be used only for those patients who have not achieved their LDL-C goal utilizing the 40-mg dose (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

PATIENTS AT HIGH RISK OF CORONARY HEART DISEASE (CHD) OR WITH EXISTING CHD

The usual starting dose of ZOCOR is 40 mg/day given as a single dose in the evening in patients at high risk of CHD (with or without hyperlipidemia), i.e., patients with diabetes, history of stroke or other cerebrovascular disease, peripheral vessel disease, or with existing CHD. Drug therapy can be initiated simultaneously with diet and exercise.

PATIENTS WITH HYPERLIPIDEMIA (WHO ARE NOT IN THE RISK CATEGORIES ABOVE)

The patient should be placed on a standard cholesterol-lowering diet before receiving ZOCOR and should continue on this diet during treatment with ZOCOR.

The usual starting dose is 20 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 10 mg of ZOCOR. Adjustments of dosage, if required, should be made as specified above.

PATIENTS WITH HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Based on the results of a controlled clinical study, the recommended dosage for patients with homozygous familial hypercholesterolemia is ZOCOR 40 mg/day in the evening or 80 mg/day in 3 divided doses of 20 mg, 20 mg, and an evening dose of 40 mg. ZOCOR should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

CONCOMITANT THERAPY

ZOCOR is effective alone or in combination with bile acid sequestrants.

In patients taking cyclosporine, danazol, gemfibrozil, or other fibrates (except fenofibrate) concomitantly with ZOCOR, the dose of ZOCOR should not exceed 10 mg/day. In patients taking amiodarone or verapamil concomitantly with ZOCOR, the dose of ZOCOR should not exceed 20 mg/day. In patients taking diltiazem concomitantly with ZOCOR, the dose of ZOCOR should not exceed 40 mg/day. (See PRECAUTIONS, *Myopathy/Rhabdomyolysis* and DRUG INTERACTIONS).

DOSAGE IN RENAL INSUFFICIENCY

Because ZOCOR 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.

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.

CONTRAINDICATIONS

- Hypersensitivity to any component of this preparation.
- Active liver disease or unexplained persistent elevations of serum transaminases.
- Pregnancy and nursing (see PRECAUTIONS, PREGNANCY and NURSING MOTHERS).

PRECAUTIONS

Myopathy/Rhabdomyolysis
Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10X the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Predisposing factors for myopathy include advanced age (≥65 years), female gender, uncontrolled hypothyroidism, and renal impairment.

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

  Potent inhibitors of CYP3A4 e.g., itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, or nefazodone, particularly with higher doses of simvastatin (see DRUG INTERACTIONS, *CYP3A4 Interactions)*.

  Other drugs:
  Gemfibrozil or other fibrates (except fenofibrate), particularly with higher doses of simvastatin (see DRUG INTERACTIONS, *Interactions with lipid-lowering drugs that 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.

  Cyclosporine or danazol particularly with higher doses of simvastatin, (see DRUG INTERACTIONS, *Other drug interactions).*

  Amiodarone with higher doses of simvastatin (see DRUG INTERACTIONS, *Other drug interactions*). In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone.

Calcium channel blockers

- **Verapamil with higher doses of simvastatin** (see DRUG INTERACTIONS, *Other drug interactions*)
- **Diltiazem: In a clinical trial** patients on diltiazem treated concomitantly with simvastatin 80 mg had an increased risk of myopathy. In clinical studies, the risk of myopathy in patients taking simvastatin 40 mg with diltiazem was similar to that in patients taking simvastatin 40 mg without diltiazem (see DRUG INTERACTIONS, *Other drug interactions*).
- **Amlodipine:** In a clinical trial, patients on amlodipine treated concomitantly with simvastatin 80 mg had a slightly increased risk of myopathy. The risk of myopathy in patients taking simvastatin 40 mg was not increased by concomitant amlodipine (see DRUG INTERACTIONS, *Other drug interactions*).

Fusidic acid: Patients on fusidic acid treated concomitantly with simvastatin may have an increased risk of myopathy (see DRUG INTERACTIONS, *Other drug interactions*; CLINICAL PHARMACOLOGY, PHARMACOKINETICS).

Niacin (≥1 g/day): see DRUG INTERACTIONS, *Interactions with lipid-lowering drugs that can cause myopathy when given alone*.

- **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 ZOCOR. 24,747 (approximately 60%) of whom were enrolled in studies with a median follow-up of at least 4 years, the incidence of myopathy was approximately 0.03%, 0.08% and 0.61% at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

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

Consequently:

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

2. The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with cyclosporine, danazol, gemfibrozil, or other fibrates (except fenofibrate). The combined use of simvastatin with gemfibrozil should be avoided unless the benefits are likely to outweigh the increased risks of this drug combination. The benefits of the use of simvastatin in patients receiving other fibrates (except fenofibrate), cyclosporine, or danazol should be carefully weighed against the risks of these drug combinations. Caution should be used when prescribing fenofibrate or niacin (≥1 g/day) 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 or niacin with simvastatin have been used without myopathy in small, short-term clinical studies with careful monitoring.

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

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

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

6. Patients on fusidic acid and simvastatin should be closely monitored. **Temporary suspension of simvastatin treatment may be considered.**

7. All patients starting therapy with simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Simvastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. The presence of these symptoms, and a CK level >10 times the upper limit of normal indicates myopathy. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved. Periodic CK determinations may be considered in patients starting therapy with simvastatin or whose dose is being increased. Periodic CK determinations are recommended for patients titrating to the 80-mg dose. There is no assurance that such monitoring will prevent myopathy.

8. 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.

HEPATIC EFFECTS

In clinical studies, persistent increases (to more than 3X ULN) in serum transaminases have occurred in a few adult patients who received simvastatin. 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 (LFTs) prior to therapy with simvastatin and/or consumed substantial quantities of alcohol.

In 4S, 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%]). The frequency of single elevations of SGPT (ALT) to 3X 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=2,221) and 5 in the placebo group (n=2,223). Of the 1986 simvastatin patients in 4S with normal LFTs at baseline, only 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. 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 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, in which 20,536 patients were randomized to receive ZOCOR 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 ZOCOR and 0.09% (n=9) for patients treated with placebo.

It is recommended that LFTs be performed before treatment begins and thereafter when clinically indicated. Patients titrated to the 80-mg dose should receive an additional test prior to titration, 3 months after titration to the 80-mg dose, and periodically thereafter (e.g., semiannually) for the first year of treatment. Special attention should be paid to patients who develop elevated serum transaminase levels,

and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3X ULN and are persistent, the drug should be discontinued.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver 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 interruption of treatment was not required.

OPHTHALMIC EVALUATIONS

In the absence of any drug therapy, an increase in the prevalence of lens opacities with time is expected as a result of aging. Current long-term data from clinical studies do not indicate an adverse effect of simvastatin on the human lens.

PREGNANCY

ZOCOR is contraindicated during pregnancy.

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 ZOCOR 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 ZOCOR or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with ZOCOR 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, ZOCOR should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with ZOCOR should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see CONTRAINDICATIONS).

NURSING MOTHERS

It is not known whether simvastatin or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions, women taking ZOCOR should not breast–feed their infants (see CONTRAINDICATIONS).

PEDIATRIC USE

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; SIDE EFFECTS) Adolescent females should be counseled on appropriate contraceptive methods while on simvastatin therapy (see CONTRAINDICATIONS; PRECAUTIONS, PREGNANCY). Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

ELDERLY

For patients over the age of 65 years who received simvastatin in controlled clinical studies, efficacy, as assessed by reduction in total-C and LDL-C, appeared similar to that seen in the population as a whole, and there was no apparent increase in the overall frequency 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.

DRUG INTERACTIONS

CYP3A4 Interactions

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. Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of simvastatin.

See PRECAUTIONS, *Myopathy/Rhabdomyolysis*.

Itraconazole
Ketoconazole
Erythromycin
Clarithromycin
Telithromycin
HIV protease inhibitors
Nefazodone

Interactions with lipid-lowering drugs that can cause myopathy when given alone

The risk of myopathy is also increased by the following lipid-lowering drugs that are not potent inhibitors of CYP3A4, but which can cause myopathy when given alone.

See PRECAUTIONS, *Myopathy/Rhabdomyolysis.*

Gemfibrozil
Other fibrates(except fenofibrate)

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.

Niacin (nicotinic acid) (≥1 g/day)

Other drug interactions

Cyclosporine or Danazol: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine or danazol particularly with higher doses of simvastatin (see PRECAUTIONS, Myopathy/Rhabdomyolysis).

Amiodarone: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone with higher doses of simvastatin (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

Calcium channel blockers:

- Verapamil: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of verapamil with higher doses of simvastatin (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).
- Diltiazem: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of diltiazem with simvastatin 80 mg (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).
- Amlodipine: Patients on amlodipine treated concomitantly with simvastatin 80 mg have a slightly increased risk of myopathy (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

Fusidic Acid: Patients on fusidic acid treated concomitantly with simvastatin may have an increased risk of myopathy (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*; CLINICAL PHARMACOLOGY, PHARMACOKINETICS).

Other interactions
Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma levels of drugs metabolized by CYP3A4. The effect of typical consumption (one 250-ml glass daily) is minimal (13% increase in active plasma HMG-CoA reductase inhibitory activity as measured by the area under the concentration-time curve) and of no clinical relevance. However, very large quantities (over 1 liter daily) significantly increase the plasma levels of HMG-CoA reductase inhibitory activity during simvastatin therapy and should be avoided (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

COUMARIN DERIVATIVES

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 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. 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 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.

SIDE EFFECTS

ZOCOR is generally well-tolerated; for the most part side effects have been mild and transient in nature. Less than 2% of patients were discontinued from controlled clinical studies due to side effects attributable to ZOCOR.

In the pre-marketing controlled clinical studies, adverse effects occurring with a frequency of 1% or more and considered by the investigator as possibly, probably or definitely drug related were: abdominal pain, constipation and flatulence. Other side effects occurring in 0.5 - 0.9% of patients were asthenia and headache.

Myopathy has been reported rarely.

In HPS involving 20,536 patients treated with 40 mg/day of ZOCOR (n=10,269) or placebo (n=10,267), the safety profiles were comparable between patients treated with ZOCOR and patients treated with placebo over the mean 5 years of the study. In this mega-trial, only serious adverse effects and discontinuations due to any adverse effects were recorded. Discontinuation rates due to side effects were comparable (4.8% in patients treated with ZOCOR compared with 5.1% in patients treated with placebo). The incidence of myopathy was <0.1% in patients treated with ZOCOR. Elevated transaminases (>3X ULN confirmed by repeat test) occurred in 0.21% (n=21) of patients treated with ZOCOR compared with 0.09% (n=9) of patients treated with placebo.

In 4S involving 4,444 patients treated with 20-40 mg/day of ZOCOR (n=2,221) or placebo (n=2,223), the safety and tolerability profiles were comparable between treatment groups over the median 5.4 years of the study.

The following additional side effects were reported either in uncontrolled clinical studies or in marketed use: nausea, diarrhea, rash, dyspepsia, pruritus, alopecia, dizziness, muscle cramps, myalgia, pancreatitis, paresthesia, peripheral neuropathy, memory impairment, insomnia, vomiting and anemia. Rarely rhabdomyolysis and hepatitis/jaundice, and very rarely hepatic failure have occurred. An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, ESR increased, arthritis, arthralgia, urticaria, photosensitivity, fever, flushing, dyspnea, and malaise.

LABORATORY TEST FINDINGS

Marked and persistent increases of serum transaminases have been reported infrequently. Elevated alkaline phosphatase and γ-glutamyl transpeptidase have been reported. Liver function test abnormalities generally have been mild and transient. Increases in serum CK levels, derived from skeletal muscle, have been reported (see PRECAUTIONS).

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 ZOCOR was generally similar to that of the group treated with placebo (see PRECAUTIONS, PEDIATRIC USE).

OVERDOSAGE

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.

AVAILABILITY

Tab. ZOCOR® (simvastatin, USP) is available in the strength of 10, 20, and 40 mg pack of (1 x 10's strip).

STORAGE

Store below 30°C (86°F). Avoid transient temperatures above 50°C (122°F).