PHYSICIANS CIRCULAR

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ZOCOR®

(simvastatin)

ZOCOR (simvastatin) 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 non-fatal 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 non-fatal 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 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 trial 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.

INDICATIONS

Therapy with lipid-altering agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when the response to diet and other nonpharmacological measures alone has been inadequate.

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

In patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, ZOCOR is indicated to:

- Reduce the risk of total mortality by reducing CHD deaths;
- Reduce the risk of non-fatal myocardial infarction and stroke;
- Reduce the need for coronary and non-coronary revascularization procedures.

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 lla), or combined (mixed) hyperlipidemia (Fredrickson type llb), 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 also indicated as an adjunct to diet and other non-dietary measures for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) to reduce elevated total-C, LDL-C and apo B.

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. Due to the increased risk of myopathy, including rhabdomyolysis, particularly during the first year of treatment, use of the 80-mg dose of ZOCOR 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. Patients unable to achieve their LDL-C goal utilizing the 40-mg dose of ZOCOR 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 (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

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

Patients with coronary heart disease can be treated with a starting dose of 20 mg/day given as a single dose in the evening. Patients at high risk for a CHD event due to existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease have been shown to benefit from 40 mg/day and can be started at this dose.

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 10 mg/day given as a single dose in the evening. Patients who require a reduction in LDL-C (more than 45%) may be started at 40 mg/day given as a single dose in the evening. 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. The 80-mg dose is only recommended when the benefits are expected to outweigh the potential risks (see above; CONTRAINDICATIONS; PRECAUTIONS, *Myopathy/Rhabdomyolysis*). 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.

In patients taking lomitapide concomitantly with ZOCOR, the dose of ZOCOR should not exceed 40 mg/day (see PRECAUTIONS, *Myopathy/Rhabdomyolysis* and DRUG INTERACTIONS).

CONCOMITANT THERAPY

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

In patients taking ZOCOR concomitantly with fibrates other than gemfibrozil (see CONTRAINDICATIONS) or fenofibrate, the dose of ZOCOR should not exceed 10 mg/day. In patients taking amiodarone, verapamil, diltiazem, or products containing elbasvir or grazoprevir concomitantly with ZOCOR, the dose of ZOCOR should not exceed 20 mg/day. In patients taking amlodipine 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.

CONTRAINDICATIONS

- Hypersensitivity to any component of this preparation.
- Active liver disease or unexplained persistent elevations of serum transaminases.
- Pregnancy and nursing (see also PRECAUTIONS, PREGNANCY and NURSING MOTHERS).
- Concomitant administration of potent CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone and drugs containing cobicistat) (see PRECAUTIONS, *Myopathy/Rhabdomyolysis* and DRUG INTERACTIONS).
- Concomitant administration of gemfibrozil, cyclosporine, or danazol (see PRECAUTIONS, *Myopathy/Rhabdomyolysis* and DRUG INTERACTIONS).

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 (i.e., elevated simvastatin and simvastatin acid plasma levels), which may be due, in part, to interacting drugs that interfere with simvastatin metabolism and/or transporter pathways (see DRUG INTERACTIONS). Predisposing factors for myopathy include advanced age (≥ 65 years), female gender, uncontrolled hypothyroidism, and renal impairment.

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%.

The risk of myopathy is greater in patients on simvastatin 80 mg compared with other statin-based therapies with similar LDL-C-lowering efficacy. Due to the increased risk of myopathy, including rhabdomyolysis, particularly during the first year of treatment, use of the 80-mg dose of ZOCOR 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. Patients unable to achieve their LDL-C goal utilizing the 40-mg dose of ZOCOR 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. In patients taking simvastatin 80 mg for whom an interacting agent is needed, a lower dose of simvastatin or an alternative statin-based regimen with less potential for drug-drug interactions should be used (see below; DOSAGE AND ADMINISTRATION; CONTRAINDICATIONS).

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 (see SIDE EFFECTS). Periodic CK determinations may be considered in patients starting therapy with simvastatin or whose dose is being increased. Periodic CK determinations are recommended for patients titrating to the 80-mg dose. There is no assurance that such monitoring will prevent myopathy.

Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. Therapy with simvastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

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

Prescribing recommendations for interacting agents are summarized in the table below (see also DOSAGE AND ADMINISTRATION; CONTRAINDICATIONS; DRUG INTERACTIONS).

TABLE 1
Drug Interactions Associated with Increased
Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Potent CYP3A4 inhibitors, e.g.,: Itraconazole Ketoconazole Posaconazole Voriconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Boceprevir Telaprevir Nefazodone Cyclosporine Danazol Gemfibrozil	Contraindicated with simvastatin
Other fibrates (except fenofibrate)	Do not exceed 10 mg simvastatin daily
Fusidic acid	Is not recommended with simvastatin.
Niacin (≥ 1 g/day)	For Asian patients, not recommended with Simvastatin
Amiodarone Verapamil Diltiazem Elbasvir Grazoprevir	Do not exceed 20 mg simvastatin daily
Amlodipine	Do not exceed 40 mg simvastatin daily
Daptomycin	Is not recommended with simvastatin.
Grapefruit juice	Avoid grapefruit juice

Drug Interactions

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

Contraindicated Drugs

Potent inhibitors of CYP3A4: Concomitant use with medicines labeled as having a potent inhibitory effect on CYP3A4 at therapeutic doses **(e.g., itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone, or drugs containing cobicistat)** is contraindicated. If short-term treatment with potent CYP3A4 inhibitors is unavoidable, therapy with simvastatin should be suspended during the course of treatment (see CONTRAINDICATIONS; DRUG INTERACTIONS).

Gemfibrozil, cyclosporine or danazol: Concomitant use of these drugs with simvastatin is contraindicated (see CONTRAINDICATIONS; DRUG INTERACTIONS, *Other drug interactions*).

Other Drugs

- **Fusidic acid:** Patients on fusidic acid treated concomitantly with simvastatin may have an increased risk of myopathy/rhabdomyolysis (see DRUG INTERACTIONS, *Other drug interactions*). Co-administration with fusidic acid is not recommended. In patients where the use of systemic fusidic acid is considered essential, simvastatin should be discontinued throughout the duration of fusidic acid treatment. In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of simvastatin and fusidic acid should only be considered on a case-by-case basis under close medical supervision.

- **Other fibrates: The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with fibrates other than gemfibrozil (see CONTRAINDICATIONS) or fenofibrate.** When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent. Caution should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone. Addition of fibrates to simvastatin typically provides little additional reduction in LDL-C, but further reductions of TG and further increases in HDL-C may be obtained. Combinations of fibrates with simvastatin have been used without myopathy in small short-term clinical studies with careful monitoring (see DRUG INTERACTIONS).

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

- **Calcium channel blockers**
  - **Verapamil**: **The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with verapamil** (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. **The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with 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 (see DRUG INTERACTIONS, *Other drug interactions*). **The dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with amlodipine.**

- **Lomitapide**: **The dose of simvastatin should not exceed 40 mg daily in patients with HoFH receiving concomitant medication with lomitapide** (see DRUG INTERACTIONS, *Other drug interactions*).

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

- **Inhibitors of Breast Cancer Resistant Protein (BCRP):** Concomitant administration of products that are inhibitors of BCRP (e.g., elbasvir and grazoprevir) may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy; therefore, a dose adjustment of simvastatin may be necessary. Co-administration of elbasvir and grazoprevir with simvastatin has not been studied; however, **the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with products containing elbasvir or grazoprevir** (see DRUG INTERACTIONS, *Other drug interactions*).

- **Niacin (≥ 1 g/day):** Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥ 1 g/day) of niacin. In a clinical trial (median follow-up 3.9 years) involving patients at high risk of cardiovascular disease and with well-controlled LDL-C levels on simvastatin 40 mg/day with or without ezetimibe 10 mg, there was no incremental benefit on cardiovascular outcomes with the addition of lipid-modifying doses (≥ 1 g/day) of niacin. Therefore, the benefit of the combined use of simvastatin with niacin should be carefully weighed against the potential risks of the combination. In addition, in this trial, the incidence of myopathy was approximately 0.24% for Chinese patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg compared with 1.24% for Chinese patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg coadministered with extended-release niacin/laropiprant 2 g/40 mg. **While the only Asian population assessed in this clinical trial was Chinese, because the incidence of myopathy is higher in Chinese than in non-Chinese patients, coadministration of simvastatin with lipid modifying doses (≥ 1 g/day) of niacin is not recommended in Asian patients** (see DRUG INTERACTIONS, *Other drug interactions*).

- **Daptomycin:** Reports of myopathy and/or rhabdomyolysis have been observed with HMG-CoA reductase inhibitors coadministered with daptomycin. Caution should be used when prescribing HMG-CoA reductase inhibitors with daptomycin, as either agent can cause myopathy and/or rhabdomyolysis when given alone. Consideration should be given to suspending ZOCOR temporarily in patients taking daptomycin (see DRUG INTERACTIONS, *Other drug interactions*).

Aggravation of Myasthenia Gravis/Ocular Myasthenia

Statins may in rare instances aggravate the conditions in patients with myasthenia gravis or ocular myasthenia (see SIDE EFFECTS). ZOCOR should be used with caution in patients with these conditions.

HEPATIC EFFECTS

In clinical studies, persistent increases (to more than 3X the 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 the ULN, over the course of the study, was not significantly different between the simvastatin and placebo groups (14 [0.7%] vs.12 [0.6%]). The frequency of single elevations of SGPT (ALT) to 3X the ULN was significantly higher in the simvastatin group in the first year of the study (20 vs. 8, p=0.023), but not thereafter. Elevated transaminases resulted in the discontinuation of 8 patients from therapy in the simvastatin group (n=2,221) and 5 in the placebo group (n=2,223). Of the 1986 simvastatin treated patients in 4S with normal liver function tests (LFTs) at baseline, only 8 (0.4%) developed consecutive LFT elevations to >3X the ULN and/or were discontinued due to transaminase elevations during the 5.4 years (median follow-up) of the study. All of the patients in this study received a starting dose of 20 mg of simvastatin; 37% were titrated to 40 mg.

In 2 controlled clinical studies in 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 liver function tests 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 three times the ULN and are persistent, the drug should be discontinued. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

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 treatment with ZOCOR, promptly interrupt therapy. If an alternate etiology is not found, do not restart ZOCOR.

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 in children have not been established.

ZOCOR is not recommended for pediatric use at this time.

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

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

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

Contraindicated drugs

Concomitant use of the following drugs is contraindicated:

Potent Inhibitors of CYP3A4: Simvastatin 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 increase the risk of myopathy by reducing the elimination of simvastatin. Concomitant use of drugs labeled as having a potent inhibitory effect on CYP3A4 (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone, drugs containing cobicistat) is contraindicated (see CONTRAINDICATIONS; PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

Gemfibrozil, Cyclosporine or Danazol: see CONTRAINDICATIONS; PRECAUTIONS, *Myopathy/Rhabdomyolysis*.

Other drug interactions

Other Fibrates: The risk of myopathy is increased by gemfibrozil (see CONTRAINDICATIONS) and other fibrates (except fenofibrate); these lipid-lowering drugs can cause myopathy when given alone. When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent (see CONTRAINDICATIONS; PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

Fusidic Acid: The risk of myopathy/rhabdomyolysis may be increased by concomitant administration of fusidic acid (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

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

Calcium Channel Blockers: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of verapamil, diltiazem, or amlodipine (see DOSAGE AND ADMINISTRATION; PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

Lomitapide: The risk of myopathy/rhabdomyolysis may be increased by concomitant administration of lomitapide (see DOSAGE AND ADMINISTRATION; PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

Moderate Inhibitors of CYP3A4: Patients taking other medicines labeled as having a moderate inhibitory effect on CYP3A4 concomitantly with simvastatin, particularly higher simvastatin doses, may have an increased risk of myopathy (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

Inhibitors of the Transport Protein OATP1B1: Simvastatin acid is a substrate of the transport protein OATP1B1. Concomitant administration of medicinal products that are inhibitors of the transport protein OATP1B1 may lead to increased plasma concentrations of simvastatin acid and an increased risk of myopathy (see CONTRAINDICATIONS; PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

Inhibitors of Breast Cancer Resistant Protein (BCRP): Simvastatin is a substrate of the efflux transporter BCRP. Concomitant administration of products that are inhibitors of BCRP (e.g., elbasvir and grazoprevir) may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy. When coadministering simvastatin with an inhibitor of BCRP, a dose adjustment of simvastatin may be necessary (see DOSAGE AND ADMINISTRATION; PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

Niacin (nicotinic acid) (≥ 1 g/day): Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥ 1 g/day) of niacin (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

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

Daptomycin: The risk of myopathy and/or rhabdomyolysis may be increased by coadministration of HMG-CoA reductase inhibitors and daptomycin (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

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, because large quantities significantly increase the plasma levels of HMG-CoA reductase inhibitory activity, grapefruit juice should be avoided during simvastatin therapy (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 (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

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, lichen planus, dyspepsia, pruritus, alopecia, dizziness, muscle cramps, myalgia, pancreatitis, paresthesia, peripheral neuropathy, insomnia, depression, vomiting and anemia, erectile dysfunction, and interstitial lung disease. Rarely rhabdomyolysis and hepatitis/jaundice, and very rarely fatal and non-fatal hepatic failure have occurred.

There have been very rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: anaphylaxis, angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, ESR increased, arthritis, arthralgia, urticaria, photosensitivity, fever, flushing, dyspnea and malaise.

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, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Aggravation of myasthenia gravis or ocular myasthenia associated with statin use has been reported (see PRECAUTIONS, *Aggravation of Myasthenia Gravis/Ocular Myasthenia*).

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).

Increases in HbA1c and fasting serum glucose levels have been reported with statins, including ZOCOR.

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

ZOCOR Tablet is available in packs of 30's as 10 mg and 20 mg.

STORAGE

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

Product Registrant:
Organon Singapore Pte. Ltd.
150 Beach Road
#36-01/08 Gateway West
Singapore 189720

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ORGANON