LOCAL PRODUCT CIRCULAR

Tablets

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 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%).

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

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

Although cholesterol is the precursor of all steroid hormones, simvastatin has not been shown to have any clinical effect on steroidogenesis. Simvastatin caused no increase in biliary lithogenicity and, therefore, would not be expected to increase the incidence of gallstones.

CLINICAL STUDIES

ZOCOR has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from VLDL and is catabolized predominantly by the high affinity LDL receptor. The mechanism of the LDL-C lowering effect of ZOCOR may involve both reduction of VLDL-cholesterol concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL-C. Apo B also falls substantially during treatment with ZOCOR. Since each LDL particle contains one molecule of apo B, and since little apo B is found in other lipoproteins, this strongly suggests that ZOCOR does not merely cause cholesterol to be lost from LDL, but also reduces the concentration of circulating LDL particles. In addition, ZOCOR increases HDL-C and reduces plasma TG. As a result of these changes the ratios of total-C to HDL-C and LDL-C to HDL-C are reduced.

The involvement of LDL-C in atherogenesis has been well-documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological studies have established that high total-C, LDL-C, and apo B are risk factors for coronary heart disease, while high HDL-C and apo A-I are associated with decreased risk.

Coronary Heart Disease

In the Scandinavian Simvastatin Survival Study (4S), the effect of therapy with ZOCOR on total mortality was assessed in 4,444 patients with CHD and baseline total cholesterol 212-309 mg/dL (5.5-8.0 mmol/L). In this multicenter, randomized, double-blind, placebo-controlled study, patients with angina or a previous myocardial infarction (MI) were treated with diet, standard care and either ZOCOR 20-40 mg daily (n=2,221) or placebo (n=2,223) for a median duration of 5.4 years. Over the course of the study, treatment with ZOCOR led to mean reductions in total-C, LDL-C, and TG of 25%, 35%, and 10%, respectively, and a mean increase in HDL-C of 8%. ZOCOR reduced the risk of death (Figure 1) by 30%, p=0.0003 (182 deaths in the ZOCOR group vs 256 deaths in the placebo group). The risk of CHD death was reduced by 42%, p=0.00001 (111 vs 189). ZOCOR also decreased the risk of having major coronary events (CHD death plus hospital-verified and silent non-fatal MI) (Figure 2) by 34%, p<0.00001 (431 patients vs 622 patients with one or more events). The risk of having a hospital-verified non-fatal MI was reduced by 37%. ZOCOR reduced the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37%, p<0.00001 (252 patients vs 383 patients). Furthermore, ZOCOR significantly reduced the risk of fatal plus non-fatal cerebrovascular events (stroke and transient ischemic attacks) by 28%, (p=0.033, 75 patients vs 102 patients). There was no statistically significant difference between groups in non-cardiovascular mortality. ZOCOR reduced the risk of major coronary events to a similar extent across the range of baseline total and LDL-C levels. The risk of death in patients ≥60 years of age was decreased by 27%, and in patients <60 years of age by 37% (p<0.01 in both age groups). Because there were only 53 female deaths, the effect of ZOCOR on mortality in women could not be adequately assessed. However, ZOCOR lessened the risk of having major coronary events by 34% (p=0.012, 60 women vs 91 women with one or more event). In patients with diabetes mellitus the risk of major coronary events was reduced by 55%, p=0.002 (24 patients vs 44 patients).

Figure 1

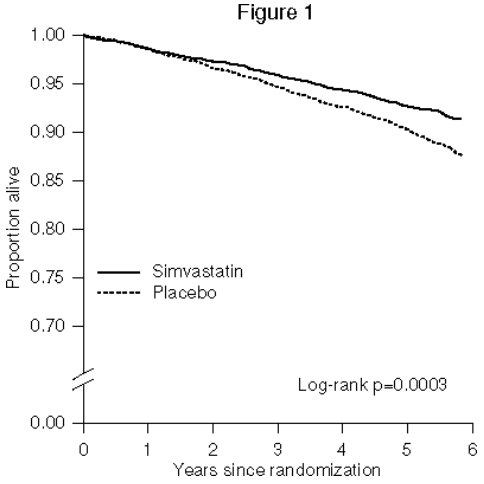
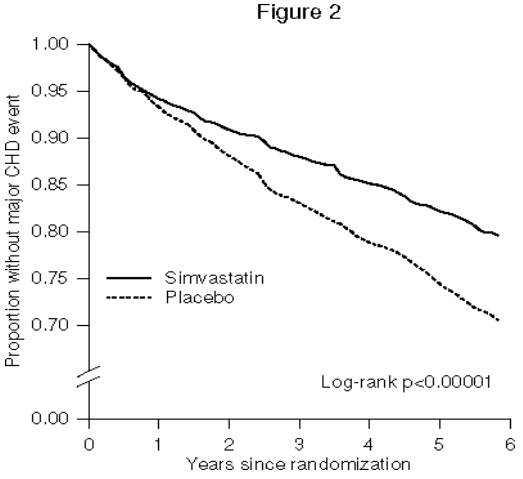


Figure 2



High Risk of Coronary Heart Disease (CHD) or Existing Coronary Heart Disease

In the Heart Protection Study (HPS), the effects of therapy with ZOCOR 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. In this multicenter, randomized, double-blind, placebo- controlled study, 10,269 patients were treated with ZOCOR 40 mg/day and 10,267 patients were treated with placebo for a mean duration of 5 years. At baseline, 6,793 patients (33%) had LDL-C levels below 116 mg/dL; 5,063 patients (25%) had levels between 116 mg/dL and 135 mg/dL; and 8,680 patients (42%) had levels greater than 135 mg/dL.

Treatment with ZOCOR 40 mg/day compared with placebo reduced the risk of total mortality by 13 % (p=0.0003) due to an 18% reduction in CHD deaths (p=0.0005). ZOCOR also decreased the risk of major coronary events (a composite endpoint comprised of non-fatal MI or CHD death) by 27% (p<0.0001). 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% (p<0.0001) and 16% (p=0.006), respectively. ZOCOR reduced the risk of stroke by 25% (p<0.0001), attributable to a 30% reduction in ischemic stroke (p<0.00001). Furthermore, ZOCOR reduced the risk of hospitalization for angina pectoris by 17% (p<0.00001). 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% (p=0.0293). 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, 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.

Angiographic Studies

The Multicenter Anti-Atheroma Study used quantitative coronary angiography to assess the effect of therapy with ZOCOR on coronary atherosclerosis in hypercholesterolemic men and women with coronary heart disease. In this randomized, double-blind, controlled clinical trial, 404 patients with total cholesterol values of 212 to 308 mg/dL (5.5 to 8.0 mmol/L) and a mean

baseline LDL value of 170 mg/dL (4.4 mmol/L) were treated with conventional measures and with ZOCOR 20 mg/day or placebo. Angiograms were evaluated at baseline, and at two and four years. A total of 347 patients had a baseline angiogram and at least one follow-up angiogram. In the patients who received placebo, coronary atherosclerotic lesions worsened in a near-linear manner. In contrast, ZOCOR significantly slowed the progression of lesions as measured in the final angiogram by the mean change per patient in minimum (p=0.005) and mean (p=0.026) lumen diameters (co-primary endpoints, indicating focal and diffuse disease, respectively), as well as in percent diameter stenosis (p=0.003). ZOCOR also significantly decreased the proportion of patients with new lesions (13% ZOCOR vs 24% placebo, p=0.009) and with new total occlusions (5% vs 11%, p=0.04). The mean change per-patient in mean and minimum lumen diameters calculated by comparing angiograms in the subset of 274 patients who had matched angiographic projections at baseline, two and four years is presented below (Figures 3 and 4).

Figure 3

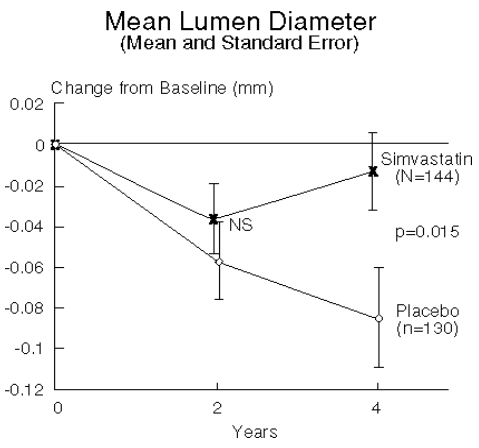
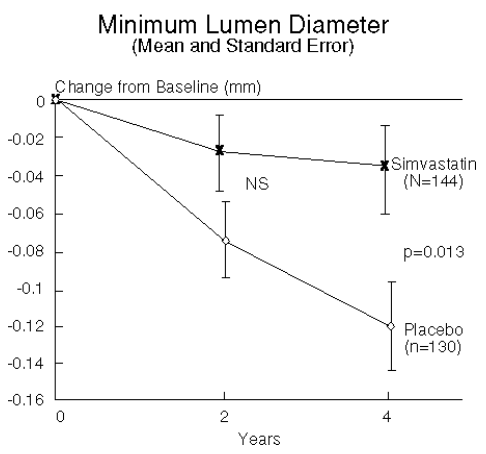


Figure 4



Primary Hypercholesterolemia and Combined Hyperlipidemia (Fredrickson type IIa and IIb)
The results of studies depicting the dose response to simvastatin in patients with primary hypercholesterolemia and combined (mixed) hyperlipidemia are presented in Table 1:

TABLE 1
Dose Response in Patients with Primary Hypercholesterolemia and Combined (mixed) Hyperlipidemia
(Mean Percent Change from Baseline After 6 to 24 Weeks)

TREATMENT	N	TOTAL-C	LDL-C	HDL-C	TG*
Lower Dose Comparative Study					
ZOCOR 5 mg**	109	-19	-26	10	-12
ZOCOR 10 mg**	110	-23	-30	12	-15
Scandinavian Simvastatin Survival Study					
Placebo	2223	-1	-1	0	-2
ZOCOR 20 mg**	2221	-28	-38	8	-19
Upper Dose Comparative Study					
ZOCOR 40 mg**	433	-31	-41	9	-18

ZOCOR 80 mg**	664	-36	-47	8	-24
Multicenter Combined Hyperlipidemia Study					
Placebo	125	1	2	3	-4
ZOCOR 40 mg**	123	-25	-29	13	-28
ZOCOR 80 mg**	124	-31	-36	16	-33

* Median percent change
** In the evening

In the Upper Dose Comparative Study, one third of patients obtained a reduction in LDL-C of 53% or more at the 80 mg dose. The percent reduction in LDL-C was essentially independent of the baseline level. In contrast, the percent reduction in triglycerides was related to the baseline level of TG. Of the 664 patients randomized to 80 mg, 475 patients with plasma TG ≤ 2.25 mmol/L (200 mg/dL) had a median reduction in TG of 21%, while in 189 patients with hypertriglyceridemia (> 2.25 mmol/L), the median reduction in TG was 36%. In these studies, patients with TG > 4.0 mmol/L (350 mg/dL) were excluded.

In the Multicenter Combined Hyperlipidemia randomized, 3-period crossover study, 130 patients with combined hyperlipidemia (LDL-C>130 mg/dL and TG: 300-700 mg/dL) were treated with placebo, ZOCOR 40, and 80 mg/day for 6 weeks. In a dose-dependent manner ZOCOR 40 and 80 mg/day, respectively, decreased mean LDL-C by 29 and 36% (placebo: 2%) and median TG levels by 28 and 33% (placebo: 4%), and increased mean HDL-C by 13 and 16% (placebo: 3%) and apolipoprotein A-I by 8 and 11% (placebo: 4%).

Homozygous Familial Hypercholesterolemia
In a controlled clinical study, 12 patients 15-39 years of age with homozygous familial hypercholesterolemia received simvastatin 40 mg/day in a single dose or in 3 divided doses, or 80 mg/day in 3 divided doses. The mean LDL-C reductions for the 40 mg and 80 mg doses were 14% and 25%, respectively. One patient with absent LDL-C receptor function had an LDL-C reduction of 41% with the 80 mg dose.

Clinical Studies in Pediatric Patients (10-17 years of age)
In a double-blind, placebo-controlled study, 175 patients (99 adolescent boys and 76 post-menarchal girls) 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (heFH) were randomized to simvastatin or placebo for 24 weeks (base study). Inclusion in the study required a baseline LDL-C level between 160 and 400 mg/dL and at least one parent with an LDL-C level >189 mg/dL. The dosage of simvastatin (once daily in the evening) was 10 mg for the first 8 weeks,20 mg for the second 8 weeks, and 40 mg thereafter. In a 24-week extension, 144 patients elected to continue therapy and received simvastatin 40 mg or placebo.

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

After 24 weeks of treatment, the mean achieved LDL-C value was 124.9 mg/dL (range: 64.0-289.0 mg/dL) in the ZOCOR 40 mg group compared to 207.8 mg/dL (range: 128.0-334.0 mg/dL) in the placebo group.

ZOCOR decreased the mean baseline total-C by 26.5% (placebo: 1.6% increase from baseline), LDL- C by 36.8% (placebo: 1.1% increase from baseline), median TG by 7.9% (placebo: 3.2%), and mean Apo B levels by 32.4% (placebo: 0.5%), and increased mean HDL-C by 8.3% (placebo:

3.6%).

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

PHARMACOKINETICS

Simvastatin is an inactive lactone which is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid, L-654,969, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studiesof the β-hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors). Both are measured in plasma following administration of simvastatin.

In a disposition study with ^{14}C-labeled simvastatin, 100 mg (20 µCi) of drug was administered as capsules (5 X 20 mg), and blood, urine, and feces collected. Thirteen percent of the radioactivity was recovered in the urine and 60% in feces. The latter represents absorbed drug equivalents excreted in bile as well as unabsorbed drug. Less than 0.5% of the dose was recovered in urine as HMG-CoA reductase inhibitors. In plasma, the inhibitors account for 14 percent and 28 percent (active and total inhibitors) of the AUC of total radioactivity, indicating that the majority of chemical species present were inactive or weak inhibitors.

Both simvastatin and L-654,969 are bound to human plasma proteins (95%). The major metabolites of simvastatin present in human plasma are L-654,969 and four additional active metabolites. The availability of L-654,969 to the systemic circulation following an oral dose of simvastatin was estimated using an i.v. reference dose of L-654,969; the value was found to be less than 5% of the dose. By analogy to the dog model, simvastatin is well absorbed and undergoes extensive first-pass extraction in the liver, the primary site of action, with subsequent excretion of drug equivalents in the bile. Consequently, availability of active drug to the general circulation is low.

In dose-proportionality studies utilizing doses of simvastatin of 5, 10, 20, 60, 90 and 120 mg there was no substantial deviation from linearity of AUC of inhibitors in the general circulation with an increase in dose. Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before a test meal.

The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of drug occurred after multiple dosing. In all of the above pharmacokinetic studies, the maximum plasma concentration of inhibitors occurred 1.3 to 2.4 hours post dose.

In a study of patients with severe renal insufficiency (creatinine clearance < 30 mL/min), the plasma concentrations of total inhibitors after a single dose of a related HMG-CoA reductase inhibitor were approximately two-fold higher than those in healthy volunteers.

In a study of 12 healthy volunteers, simvastatin at the maximal 80-mg dose had no effect on the metabolism of the probe CYP3A4 substrates midazolam and erythromycin. This indicates that simvastatin is not an inhibitor of CYP3A4, and therefore, is not expected to affect the plasma levels of other drugs metabolized by CYP3A4.

Although the mechanism is not fully understood, cyclosporine has been shown to increase the AUC of HMG-CoA reductase inhibitors. The increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4 and/or OATP1B1. (See CONTRAINDICATIONS)

In a pharmacokinetic study, concomitant administration of diltiazem caused a 2.7-fold increase in

exposure of simvastatin acid, presumably due to inhibition of CYP3A4. (see PRECAUTIONS,*Myopathy/Rhabdomyolysis*).

In a pharmacokinetic study, concomitant administration of amlodipine caused a 1.6-fold increase in exposure of simvastatin acid. (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

In a pharmacokinetic study, the coadministration of a single dose of niacin extended- release 2 g with simvastatin 20 mg resulted in a modest increase in the AUC of simvastatin and simvastatin acid and in the C_{max} of simvastatin acid plasma concentrations. (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

Specific pathways of fusidic acid metabolism in the liver are not known, however, interaction between fusidic acid and HMG-CoA reductase inhibitors which are metabolized by CYP3A4 can be suspected. (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Potent inhibitors of CYP3A4 can raise the plasma levels of HMG- CoA reductase inhibitory activity and increase the risk of myopathy (see CONTRAINDICATIONS, PRECAUTIONS, *Myopathy/Rhabdomyolysis*; DRUG INTERACTIONS).

INDICATIONS

REDUCTIONS IN RISK OF CHD MORTALITY AND CARDIOVASCULAR EVENTS

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.

HYPERLIPIDEMIA

- ZOCOR is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, Apo B, and TG, and to increase HDL-C in patients with primary hypercholesterolemia, heterozygous familial hypercholesterolemia or combined (mixed) hyperlipidemia when response to diet and other nonpharmacological measures is inadequate. ZOCOR therefore, lowers the LDL-C/HDL-C and the total-C/HDL-C ratios.

PEDIATRIC PATIENTS WITH HETEROZYGOUS FAMILIALHYPERCHOLESTEROLEMIA

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).

GENERAL RECOMMENDATIONS

Prior to initiating therapy with ZOCOR, secondary causes of hypercholesterolemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.

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 is only recommended in patients at high risk for cardiovascular complications who have not achieved treatment goals on lower doses and when the benefits are expected to outweigh the potential risks (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

The recommended usual starting dose is 20-40 mg once a day in the evening.

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), ie., patients with diabetes, history of stroke or other cerebrovascular disease, peripheral vessel disease, or with existing CHD. Drug therapy can be initiated simultaneously with a standard cholesterol-lowering 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 a day in the evening. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40mg/day given as single dose in the evening. Patients with mild to moderate hypercholesterolemia can be treated with a starting dose of 10mg 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. 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 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 20mg/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 (see CLINICAL PHARMACOLOGY, PHARMACOKINETICS).

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 10-40mg/day; the maximum recommended dose is 40 mg/day. Doses should be individualized according to the recommended goal of therapy (see CLINICAL PHARMACOLOGY).

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).
- 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. Therefore, the 80-mg dose of ZOCOR should only be used in patients at high risk for cardiovascular complications who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks. 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.

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by:

- persistent 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.

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; CLINICAL PHARMACOLOGY, PHARMACOKINETICS.)

Gemfibrozil, cyclosporine or danazol: Concomitant use of these drugs with simvastatin is contraindicated. (See CONTRAINDICATIONS; DRUG INTERACTIONS, CLINICAL PHARMACOLOGY, PHARMACOKINETICS.).

Other Drugs

- **Fusidic acid:** Patients on fusidic acid treated concomitantly with simvastatinmay have an increased risk of myopathy/rhabdomyolysis (see DRUG INTERACTIONS, *Other drug interactions*; CLINICAL PHARMACOLOGY, PHARMACOKINETICS). 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 or diltiazem:** In a clinical trial, patients on diltiazem treated concomitantly with simvastatin 80 mg had an increased risk of myopathy. **The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with verapamil or 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 mgcompared 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*).

Myasthenia Gravis/Ocular Myasthenia

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia (see SIDE EFFECTS). ZOCOR should be discontinued in case aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

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 (see CLINICAL PHARMACOLOGY), 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 (see CLINICAL PHARMACOLOGY), 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. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

There have been rare post marketing 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 quantitiesof 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 cyclelength in girls (see DOSAGE AND ADMINISTRATION; SIDE EFFECTS; CLINICAL PHARMACOLOGY). 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

Multiple mechanisms may contribute to potential interactions with HMG Co-A reductaseinhibitors. 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*; CLINICAL PHARMACOLOGY, PHARMACOKINETICS.

Gemfibrozil, Cyclosporine or Danazol: See CONTRAINDICATIONS; PRECAUTIONS, *Myopathy/Rhabdomyolysis*, CLINICAL PHARMACOLOGY, PHARMACOKINETICS.

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*; CLINICAL PHARMACOLOGY, PHARMACOKINETICS).

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;* CLINICAL PHARMACOLOGY, PHARMACOKINETICS).

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 drug metabolized by CYP3A4. The effect of typical consumption (one 250-ml glass daily) is minimal (13% increase in active plasma HMG- CoA reductase inhibitory activity as measured by the area under the concentration-time curve) and of no clinical relevance. However, because larger quantities significantly increase the plasma level 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 (see CLINICAL PHARMACOLOGY) 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 (see CLINICAL PHARMACOLOGY) 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, 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 clinically characterized by: persistent 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 post marketing 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).

Nervous system disorders:
Frequency 'not known': myasthenia gravis

Eye disorders:
Frequency 'not known': 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. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment.

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; CLINICAL PHARMACOLOGY).

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 10 mg is available in blister packs of 30's and 120's.
ZOCOR 20 mg is available in blister packs of 30's and 120's.
ZOCOR 40 mg is available in blister packs of 30's and 60's.

Not all pack sizes may be marketed.

PRODUCT DESCRIPTION

ZOCOR 10 mg: Peach, oval-shaped film coated tablet. One side imprinted MSD735,the other side plain.
ZOCOR 20 mg: Tan, oval-shaped film coated tablet. One side imprinted MSD740, the other side plain.
ZOCOR 40 mg: Brick Red, oval-shaped film coated tablet. One side imprintedMSD749, the other side plain.

SHELF LIFE

Please refer to the expiry date on the outer carton.

STORAGE CONDITION

ZOCOR 10 mg, 20 mg and 40 mg: Store below 30°C (86°F). Protect from moisture and light.

MANUFACTURER

Organon Pharma (UK) Limited
Shotton Lane, Cramlington Northumberland NE23 3JU
United Kingdom

PRODUCT REGISTRATION HOLDER

ORGANON MALAYSIA SDN. BHD.
39W022, Mercu 2,
No.3, Jalan Bangsar, KL Eco City,
59200 Kuala Lumpur,
Malaysia

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