SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

ZOCOR® 10 Tablet

ZOCOR® 20 Tablet

ZOCOR®40 Tablet

COMPOSITION

Each ZOCOR 10 Tablet contains 10 mg simvastatin, MSD.

Each ZOCOR 20 Tablet contains 20 mg simvastatin, MSD.

Each ZOCOR 40 Tablet contains 40 mg simvastatin, MSD.

PHARMACOLOGICAL CLASSIFICATION

A 7.5 Serum-cholesterol reducers

PHARMACOLOGICAL ACTION

ZOCOR (simvastatin, MSD) is a cholesterol-lowering agent derived synthetically from a fermentation product of Aspergillus terreus. After oral ingestion ZOCOR, which is an inactive lactone, is hydrolyzed to the corresponding beta-hydroxyacid (active form). This is a principal metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme which catalyzes the conversion of HMG-CoA to mevalonate, an early and rate limiting step in the biosynthesis of cholesterol. As a result, ZOCOR, reduces total plasma cholesterol, low-density lipoprotein (LDL)- and very low-density lipoprotein (VLDL)-cholesterol concentrations. Apolipoprotein B is also decreased. In addition, ZOCOR moderately increases high-density lipoprotein (HDL)-cholesterol and reduces plasma triglycerides.

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 4444 patients with coronary heart disease (CHD) and baseline total cholesterol 5,5-8,0 mmol/L (212-309 mg/dL). In this multicenter, randomized, double-blind, placebo-controlled study, ZOCOR reduced the risk of death by 30% (p equal to 0,0003, 182 deaths in the ZOCOR group vs 256 deaths in the placebo group), of CHD death by 42% (p equal to 0,00001, 111 vs 189), and of having a hospital-verified non-fatal myocardial infarction by 37%. Furthermore, ZOCOR reduced the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37% (p less than 0,00001, 252 patients vs 383 patients).

In a multicenter, placebo-controlled clinical trial in 404 patients using quantitative coronary angiography, ZOCOR significantly slowed the progression of lesions as measured in the final angiogram by the co-primary endpoints of the trial (mean changes in minimum lumen diameter: -0,04 mm with simvastatin vs -0,12 mm with placebo; mean changes in mean lumen diameter: -0,03 mm with simvastatin vs -0,08 mm with placebo), as well as by change from baseline in percent diameter stenosis (0,9 % simvastatin vs 3,6 % placebo). After four years, the groups also differed significantly in the proportions of patients categorized with disease progression (23 % simvastatin vs 33 % placebo) and disease regression (18 % simvastatin vs 12 % placebo). In addition, ZOCOR reduced the development of both new lesions (13 % simvastatin vs 24 % placebo) and new total occlusions (5 % vs 11 %), whereas coronary atherosclerotic lesions steadily worsened over four years in patients receiving standard care.

INDICATIONS

CORONARY HEART DISEASE

In patients with established coronary heart disease and hypercholesterolaemia unresponsive to diet.

ZOCOR is indicated to :

- Reduce the risk of total mortality by reducing coronary death;
- Reduce the risk of non-fatal myocardial infarction;
- Reduce the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting and percutaneous transluminal coronary angioplasty); and
- Slow the progression of coronary atherosclerosis.

HYPERCHOLESTEROLAEMIA

ZOCOR is indicated as an adjunct to diet for reduction of elevated total cholesterol and LDL-cholesterol in patients with primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia when response to diet and other nonpharmacological measures is inadequate.

CONTRA-INDICATIONS

Hypersensitivity to any component of this preparation.

Acute or chronic hepatic diseases or unexplained persistent elevations of serum transaminases.

Pregnancy and lactation.

WARNING

The active metabolite of ZOCOR is fetotoxic and teratogenic in rats and it should therefore not be used in female patients of childbearing potential. Use in paediatric patients is not recommended, as safety and efficacy have not been established. ZOCOR is not effective in severe hypertriglyceridaemia.

DOSAGE AND DIRECTIONS FOR USE

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

HYPERCHOLESTEROLAEMIA

The usual starting dose is 10 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 daily given as a single dose in the evening.

If LDL-cholesterol levels fall below 1,94 mmol/l (75 mg/dl) or total plasma cholesterol levels fall below 3,6 mmol/l (140 mg/dl) the dose of ZOCOR should be reduced.

CORONARY HEART DISEASE

Patients with coronary heart disease can be treated with a starting dose of 20 mg/day given as a single dose in the evening. Adjustments of dosage, if required, should be made as specified above (see **DOSAGE AND DIRECTIONS FOR USE**, HYPERCHOLESTEROLAEMIA).

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 less than 30 ml/min), dosages above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously.

Concomitant Therapy

ZOCOR is effective alone or in combination with bile acid sequestrants. When both agents are prescribed, ZOCOR should be given either 1 hour before or 4 hours after cholestyramine administration.

In patients taking cyclosporine, fibrates or niacin concomitantly with ZOCOR the maximum recommended dosage is 10 mg/day (See **SPECIAL PRECAUTIONS** - Muscle Effects).

SIDE EFFECTS AND SPECIAL PRECAUTIONS

SIDE EFFECTS

Abdominal pain and cramps, constipation, flatulence, asthenia, headache, nausea, diarrhoea, rash, dyspepsia, pruritus, anemia, fatigue, alopecia, dizziness, muscle cramps, myalgia, pancreatitis, paraesthesia, and vomiting.

Rhabdomyolysis, hepatitis / jaundice and myopathy have been reported less frequently.
Neutropenia, mass gain and peripheral neuropathy have occurred with HMG-CoA reductase inhibitors.

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

LABORATORY TEST FINDINGS

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

SPECIAL PRECAUTIONS

Hepatic Effects

In clinical trials marked persistent increases (to more than 3 times the upper limit of normal [ULN]) in serum transaminases have occurred. When ZOCOR was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels.

In the Scandinavian Simvastatin Survival Study , the number of patients with more than one transaminase elevation to more than 3 times the ULN, over the course of the study, was not significantly different between the simvastatin and placebo groups (14 [0,7%] vs. 12 [0,6%].) The frequency of single elevations of SGPT (ALT) to 3 times the ULN was significantly higher in the simvastatin group in the first year of the study (20 vs 8, p equal to 0,023), but not thereafter. Elevated transaminases resulted in the discontinuation of 8 patients from therapy in the simvastatin group (n equal to 2,221) and 5 in the placebo group (n equal to 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 more than 3 times the ULN and/or were discontinued due to transaminase elevations during the 5,4 years (median follow-up) of the study. All of the patients in this study received a starting dose of 20 mg of simvastatin; 27% were titrated to 40 mg.

In 2 controlled clinical studies in 1105 patients, the 6 month incidence of persistent hepatic transaminase elevations considered drug-related was 0,7 % and 1,8 % at the 40 and 80 mg dose respectively.

As hepatitis, evidenced by liver enzyme elevation, has also been reported, it is recommended that liver function tests be performed before treatment begins, and periodically thereafter. Patients titrated to the 80 mg dose should receive an additional test at 3 months. 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, ZOCOR should be discontinued.

ZOCOR 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 contra-indications to the use of simvastatin.

Ophthalmic Effects

In the absence of any medicine therapy, an increase in the prevalence of lens opacities with time is expected as a result of aging. Current long term data from clinical trials do not indicate a causal association between simvastatin and adverse effects on the human lens.

Muscle Effects

Simvastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as muscle pain or weakness associated with grossly elevated creatine kinase (CK)(more than 10 x the upper limit of normal [ULN]). Rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, has been reported rarely.

Myopathy caused by drug interactions

The incidence and severity of myopathy are increased by concomitant administration of HMG-CoA reductase inhibitors with drugs that can cause myopathy when given alone, such as fibrates and lipid-lowering doses(more than or equal to 1 g/day) of niacin (nicotinic acid).

Medicines which substantially inhibit the activity of the cytochrome P450 isoform 3A4 (cyclosporine, the azole antifungals itraconazole and ketoconazole, the macrolide antibiotics erythromycin and clarithromycin, HIV protease inhibitors and nefazodone) increase the risk of myopathy when used concomitantly with HMG-CoA reductase inhibitors.

Reducing the risk of myopathy

1. General measures

   Patients starting therapy with simvastatin should be advised of the risk of myopathy and told to report promptly unexplained muscle pain, tenderness or weakness. A CK level above 10 x ULN in a patient with unexplained muscle symptoms indicates myopathy. Simvastatin therapy should be discontinued if myopathy is diagnosed or suspected.

2. Measures to reduce the risk of myopathy caused by drug interactions (see above)

   The benefit and risks of using simvastatin concomitantly with immunosuppressives, fibrates or lipid lowering doses of niacin should be carefully considered, and the dose of simvastatin should generally not exceed 10 mg/day. Concomitant use of simvastatin with itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, or nefazodone is not recommended. In patients receiving cyclosporine, simvastatin should be temporarily discontinued if systemic azole derivatives antifungal therapy is required.

INTERACTIONS

Caution should be exercised in the concomitant use of ZOCOR with cyclosporine, itraconazole, ketoconazole, fibric acid derivatives, niacin, erythromycin, clarithromycin, HIV protease inhibitors or nefazodone (see **SPECIAL PRECAUTIONS**, Skeletal Muscle).

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 insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Digoxin

Simvastatin increases digoxin levels.

Propranolol

In healthy male volunteers there was a significant decrease in mean Cmax, but no change in AUC, for simvastatin total and active inhibitors with concomitant administration of single doses of ZOCOR and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.

WARNING

Caution should be exercised in the concomitant use of cyclosporine, itraconazole, ketoconazole, fibric acid derivatives, niacin, erythromycin, clarithromycin, HIV protease inhibitors or nefazodone (see **SPECIAL PRECAUTIONS**, Skeletal Muscle).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

(see **SIDE EFFECTS** and **SPECIAL PRECAUTIONS**).

General measures should be adopted and liver function should be monitored.

Treatment is symptomatic and supportive.

IDENTIFICATION

ZOCOR 10 is a peach-coloured, biconvex, oval-shaped 8,5 mm x 5 mm film coated tablet.

One side has MSD 735 and the other side is plain.

ZOCOR 20 is a round, tan coloured, film coated tablet coded with MSD 740 on one side and scored on the other. Diameter 7,99 mm.

ZOCOR 40 is a brick red, oval-shaped, film-coated tablet. One side is plain and the other side engraved MSD 749.

PRESENTATION

ZOCOR 10 and ZOCOR 20 tablets are available in blister packs of 28 tablets.

ZOCOR 40 tablets is available in blister packs of 30.

STORAGE INSTRUCTIONS

Store in a dry place below 25° C. Protect from light.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

ZOCOR 10 : W/7.5/350

ZOCOR 20 : W/7.5/351

ZOCOR 40 : 31/7.5/447

NAME AND BUSINESS ADDRESS OF THE APPLICANT

MSD(PTY) LTD

16th Road

Halfway House

1685

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