SIMVACOR FILM COATED TABLET

Ingredient(s):
Simvacor Film Coated Tablet 20mg:
Each tablet contains:
Simvastatin 20mg
Simvacor Film Coated Tablet 40mg:
Each tablet contains:
Simvastatin 40mg

Pharmacology (Summary of Pharmacodynamic and Pharmacokinetic):
1. Simvastatin is a specific inhibitor of HMG-CoA reductase, the enzyme which catalyzes the conversion of HMG-CoA to mevalonate, the rate-limiting step in cholesterol biosynthesis in the liver.
2. Inhibition of cholesterol synthesis leads to upregulation of LDL receptors and an increased in catabolism of LDL cholesterol.
3. There may also be some reduction in LDL production as a result of inhibition of hepatic synthesis of VLDL, the precursor of LDL.
4. Simvastatin is absorbed from the gastro-intestinal tract and is hydrolyzed to its active beta-hydroxy acid, as well as some other active and inactive metabolites.
5. Simvastatin undergoes extensive first-pass metabolism in the liver and <5% of the oral dose has been reported to reach the circulation as active metabolite. Simvastatin and its beta-hydroxy acid metabolite are about 95% bound to plasma protein.
6. It is mainly excreted in feces via bile as metabolites. About 10 to 15% is recovered in the urine, mainly in inactive forms. Half-life of the active metabolites is 1.9 hour.

Indication(s):
Coronary Heart Disease: Reduce the risk of death; reduce the risk of coronary death and 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 artherosclerosis, including reducing the development of new lesions and new total occlusions.
Hyperlipidemia: 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.

Dosage and Administration:
Hyperlipidaemia: 20mg as a single evening dose. Patients who require only a moderate reduction may start at 10mg. Adjust at intervals not <4 wk as required.

Coronary Heart Disease: Initially 20mg as a single evening dose. Adjust at intervals not < 4 wk as required. Max: 80mg/day as a single evening dose.
The 80mg 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.

Homozygous familial hypercholesterolemia: 40mg as a single evening dose.

<u>Concomitant Therapy</u>
In patients taking fibrates (other than gemfibrozil and fenofibrate) concomitantly with this product, the dose of this product should not exceed 10mg/day.

In patients taking amiodarone, verapamil or diltiazem concomitantly with this product, the dose of this product should not exceed 20mg/day.

In patients taking amlodipine or lipid-lowering dose of niacin (≥1g/day) concomitantly with this product , the dose of this product should not exceed 40mg/day.

Renal insufficiency: Because simvastatin 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 <30mL/min), dosage above 10mg/day should be carefully considered and, if deemed necessary, implemented cautiously.
Can be taken with meals or on an empty stomach.

Mode of Administration :
For oral use.

Contraindications:
1. Hypersensitivity to simvastatin or any HMG-CoA reductase inhibitors.
2. Active liver disease or unexplained persistent elevations of serum transaminases.
3. Pregnancy and nursing women.
4. Concomitant administration of potent CYP3A4 inhibitors (e.g itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone).
5. Concomitant administration of gemfibrozil, cyclosporine, or danazol.

Side Effect(s) / Adverse Reaction(s):
1. The most common adverse effects of therapy with simvastatin and other statins are gastro-intestinal disturbances. Other adverse effects reported include skin rashes, dizziness, blurred vision, insomnia, dysgeusia, abdominal pain, constipation, flatulence, asthenia, headache, myopathy, nausea, diarrhea, dyspepsia, pruritus, alopecia, muscle cramp, myalgia, parethesia, peripheral neuropathy, vomiting, and anemia.
2. Reversible increases in serum-aminotransferase concentrations may occur and liver function should be monitored.
3. Hepatitis and pancreatitis have been reported.
4. A hypersensitivity syndrome has been reported rarely whose features have included: angioedema, lupus-like syndrome, polymyalgia rheumatica, vasculitis, thrombocytopenia, eosinophilia, increased ESR, arthritis, arthralgia, urticaria, photosensitivity, fever, flushing, dyspnea and malaise, especially in patients taking simvastatin concurrently with immunosuppresants, fibric acid derivatives or nicotinic acid.
5. Rarely, rhabdomyolysis with acute renal failure may develop.
6. 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 non-serious and reversible upon statin discontinuation, with variable times to symptom onset (1day to years) and symptom resolution (median 3 weeks).
7. Increases in HbA1c and fasting blood glucose have been reported with statins. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.

Precaution(s) / Warning(s):
1. Special attention should be paid to patients who develop elevated serum transaminase levels and liver function tests should be repeated promptly and more frequently.
2. Myopathy/ Rhabdomyolysis:
   Simvastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as a muscle pain or weakness associated with grossly elevated creatine kinase (CK) (>10X 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, eg gemfibrozil and other fibrates, and lipid-lowering doses (≥1g/day) of niacin (nicotinic acid). In addition, the risk of myopathy appears to be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Simvastatin and other HMG-CoA reductase inhibitors are metabolized by the cytochrome P450 isoform 3A4 (CYP3A4). Certain drugs that are potent inhibitors of this metabolic pathway can raise the plasma levels of HMG-CoA reductase inhibitors and thus increase the risk of myopathy. These include cyclosporine, the antifungal azoles itraconazole and ketoconazole, the macrolide antibiotics erythromycin and clarithromycin, HIV protease inhibitors, and the antidepressant nefazodone. The risk of myopathy appears to be increased by concomitant administration of verapamil, but not by other calcium channel blockers.

   Reducing the risk of myopathy : (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□ ULN in a patient with unexplained muscle symptoms indicates myopathy. Simvastatin therapy should be discontinued if myopathy is diagnosed or suspected. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved. Of patients with rhabdomyolysis, many had complicated medical histories. Some have preexisting renal insufficiency, usually as a consequence of long-standing diabetes. In such patients, dose escalation requires caution. Also, as there are no known adverse consequences of brief interruption of therapy, treatment with simvastatin should be stopped a few days before elective major surgery and when any major acute medical or surgical condition supervenes.

   Measures to reduce the risk of myopathy caused by drug interactions:
   Physicians contemplating combined therapy with simvastatin and any of the interacting drugs should weigh the potential benefits and risks, and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CK determinations may be considered in such situations, but there is no such assurance that such monitoring will prevent myopathy.

   The combined use of simvastatin with fibrates or niacin should be avoided unless the benefit of further alteration in lipid concentrations is likely to outweigh the increased risk of this drug combination. Combinations of fibrates or niacin with low doses of simvastatin have been used without myopathy in small, short-term clinical studies with careful monitoring. Addition of these drugs to HMG-CoA reductase inhibitors typically provides little additional reduction in LDL-C, but further reductions of triglycerides and further increases in HDL-C may be obtained. If one of these drugs must be used with simvastatin, clinical experience suggests that the risk of myopathy is less with niacin than with the fibrates.

   In patients taking concomitant cyclosporine, fibrates or niacin, the dose of simvastatin should generally not exceed 10mg, as the risk of myopathy increases substantially at higher doses. Concomitant use of simvastatin with itraconazole, ketoconazole, erythromycin, or clarithromycin, HIV protease inhibitors, or nefazodone is not recommended if no alternative to a short-course with itraconazole, ketoconazole, erythromycin or clarithromycin is available, a brief suspension of simvastatin therapy can be considered as there are no known adverse consequences to brief interruptions of long-term cholesterol-lowering therapy. Concomitant use with other medicines labeled as having potent inhibitory effect on cytochrome CYP3A4 at therapeutic doses should be avoided unless the benefits of combined therapy outweigh the increased risk.
3. Opthalmic 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.
4. Laboratory 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 creatine kinase levels, derived from skeletal muscle, have been reported.
5. This drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease.
6. Use in pregnancy: Simvastatin is contraindicated during pregnancy since there is a possibility that it could interfere with fetal sterol synthesis.
7. Use in lactation: Nursing mother: It is not known whether simvastatin or its metabolites are excreted in human milk and because of the potential for serious adverse reactions, women taking simvastatin should not breastfeed their infants.
8. Use in children: Safety and effectiveness in children have not been established.
9. Use in the elderly: For patients over the age of 65 years who received simvastatin in controlled clinical studies, efficacy appeared similar to that seen in the population as a whole and there was no apparent increase in the frequency of clinical or laboratory adverse findings.

Interaction with Other Medicaments:
1. 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 or nefazodone) is contraindicated. If treatment with potent CYP3A4 inhibitors is unavoidable, therapy with simvastatin should be suspended during the course of treatment.

   Gemfibrozil, cyclosporine or danazol: Concomitant use of these drugs with simvastatin is contraindicated.

2. Other Drugs
   - Other fibrates: The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with fibrates other than gemfibrozil 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. Concurrent use of fibrates may cause severe myositis and myoglobinuria.
   - Amiodarone: In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80mg and amiodarone. The dose of simvastatin should not exceed 20mg daily in patients receiving concomitant medication with amiodarone.
   - 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.
     - Amlodipine: In a clinical trial, patients on amlodipine treated concomitantly with simvastatin 80 mg had a slightly increased risk of myopathy. The dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with amlodipine.
     - Niacin (≥1g/day): The dose of simvastatin should not exceed 40mg daily in patients receiving concomitant medication with niacin (nicotinic acid) ≥1g/day. Cases of myopathy/ rhabdomyolysis have been observed with simvastatin co-administered with lipid-modifying doses (≥1g/day) of niacin.
3. Coumarin derivatives: Bleedings and increases in prothrombin time have been reported in patients taking simvastatin and coumarin anticoagulants.
4. Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase plasma levels of simvastatin.

Pregnancy and Lactation:
Contraindicated in pregnancy and nursing mother.

Symptoms and Treatment for Overdosage, and Antidote(s):
A few cases of overdosage have been reported; no patients had any specific symptoms and all patients recovered without sequelae. The maximum dose taken was 450mg. General measures should be adopted.

Shelf-Life:
3 years from the date of manufacture.

Storage Condition(s):
Keep in a tight container. Store at temperature below 30°C. Protect from light and moisture.

Product Description and Packing(s):
Simvacor Film Coated Tablet 20mg
An orange brown color elliptical film coated tablet 

Plastic bottle of 30's.
Blister packing of 10's x 3, 10's x 10, 10's x 12 and 10's x 50.

Simvacor Film Coated Tablet 40mg
A pale orange red elliptical film coated tablet. 

Plastic bottle of 30's.
Blister packing of 10's x 3, 10's x 10, 10's x 12 and 10's x 50.

Y. S. P.

Manufacturer and Product Registration Holder :
Y.S.P. INDUSTRIES (M) SDN. BHD. (192593 U)
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