SIMVASTATIN TABLETS USP 10 / 20 mg

Simvas

COMPOSITION:
Each film-coated tablet contains:
Simvastatin USP 10 / 20mg.

Description:
Simvastatin is a cholesterol lowering agent that is derived synthetically from a fermentation product of Aspergillus terreus. It is an inhibitor of 3-hydroxy 3-methyl glutaryl Coenzyme A (HMG CoA) reductase. This enzyme catalyses the conversion of HMG CoA to mevalonate which is a rate limiting step in the biosynthesis of Cholesterol.

PHARMACOLOGY:
Pharmacology: Simvastatin is a specific inhibitor of HMG-CoA reductase, the enzyme that catalyses the conversion of HMG CoA to mevalonate. The conversion of HMG-CoA to Mevalonate is an early step in the biosynthetic pathway for cholesterol.

Simvastatin has been shown to reduce both normal and elevated LDL cholesterol concentrations. LDL is formed from very low density lipoprotein (VLDL) and is catabolized predominantly by the high affinity LDL receptor. The mechanism of the LDL - lowering effect of Simvastatin may involve both reduction of VLDL Cholesterol concentration, and induction of the LDL receptor, leading to reduced production and/or increased catabolism of LDL cholesterol.

Pharmacokinetics: Simvastatin, after absorption from gastrointestinal tract, undergoes extensive first pass metabolism in liver. As a consequence, the availability of drug to the general circulation is low and variable. Less than 5% of the oral dose has been reported to reach the circulation as the active metabolite. It is highly bound to plasma proteins (95%). Simvastatin is hydrolyzed in liver to its active beta-hydroxy acid form. Three other metabolites also have been isolated as 6-hydroxy, 6-hydroxy methyl and 6-exomethylene derivatives. Simvastatin is eliminated primarily through the faecal route which is mainly the unabsorbed fraction of the drug and forms 60% of the orally administered dose. About 10-15% of the drug is eliminated by the renal route. The half-life of the active metabolite is 1.9 hour.

INDICATIONS AND USES:
SIMVAS (Simvastatin) is indicated as an adjunct to diet in patients with primary hypercholesterolemia (Type IIa and IIb) caused by elevated low density lipoprotein cholesterol concentrations in patients with a significant risk of coronary artery disease, when the response to a diet restricted in saturated fat and cholesterol and other non pharmacological measures alone have been inadequate.

SIMVAS (Simvastatin) is also indicated for the reduction of elevated total and LDL cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb).

CONTRAINDICATIONS:
Hypersensitivity to any component of this medication. Active liver disease or unexplained persistent elevations of serum transaminases.

Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone).

Concomitant administration of gemfibrozil, cyclosporine, or danazol.

SIDE EFFECTS / ADVERSE REACTIONS:
Simvastatin is generally well tolerated. However, a few gastrointestinal symptoms have been reported viz. flatulence, diarrhoea, constipation, nausea, abdominal pain, cramps. Other adverse effects include headache, dizziness, rashes and insomnia.

Myopathy has been rarely reported

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 (1 day to years) and symptom resolution (median of 3 weeks).

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

PRECAUTIONS / WARNINGS:
General: Before instituting therapy with Simvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise and weight reduction in obese patients and to treat other underlying medical problems.

Simvastatin may cause elevation of serum creatine phosphokinase and serum transaminase levels. This should be considered in the differential diagnosis of chest pain in a patient on therapy with Simvastatin.

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

As with other statins, the risk of myopathy/rhabdomyolysis is dose related. In a clinical trial database in which 41,413 patients were treated with simvastatin, 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 simvastatin 80 mg/day (mean follow-up 6.7 years), the incidence of myopathy was approximately 1.0% compared with 0.02% for patients on 20 mg/day. Approximately half of these myopathy cases occurred during the first year of treatment. The incidence of myopathy during each subsequent year of treatment was approximately 0.1%. The risk of myopathy is greater in patients on simvastatin 80 mg compared with other statin-based therapies with similar LDL-C- lowering efficacy. Due to the increased risk of myopathy, including rhabdomyolysis, particularly during the first year of treatment, use of the 80-mg dose of simvastatin should be restricted to patients who have been taking simvastatin 80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity. Patients unable to achieve their LDL-C goal utilizing the 40- mg dose of simvastatin should not be titrated to the 80- mg dose, but should be placed on alternative LDL-C lowering treatment(s) that provides greater LDL-C lowering. In patients taking simvastatin 80 mg for whom an interacting agent is needed, a lower dose of simvastatin or an alternative statin-based regimen with less potential for drug-drug interactions should be used.

All patients starting therapy with simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Simvastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected.

The presence of these symptoms, and a CK level >10 times the upper limit of normal indicates myopathy. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved. Periodic CK determinations may be considered in patients starting therapy with simvastatin or whose dose is being increased. Periodic CK determinations are recommended for patients titrating to the 80- mg dose. There is no assurance that such monitoring will prevent myopathy.

Prescribing recommendations for interacting agents are summarized in the table below:

Drug Interactions associated with the Increased risk of Myopathy/Rhabdomyolysis	
Interacting Agents	**Prescribing recommendations**
Potent CYP3A4 inhibitors, e.g Itraconazole Ketoconazole Posaconazole Voricomzole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Boceprevir Telaprevir Nefazodone Cyclosporine Danazol Gemfibrozil	Contraindicated with simvastatin
Other fibrates (except fenofibrate)	Do not exceed 10 mg simvastatin daily.
Fusidic acid	Is not recommended with simvastatin.
Amiodarone Verapamil Dilitazem	Do not exceed 20mg simvastatin daily.
Amlodipine	Do not exceed 40mg simvastatin daily.
Grape fruit juice	Avoid grape fruit juice

Warnings: Liver Dysfunction: Persistent increase in serum transaminase has occurred in 1 % of patients who received Simvastatin in clinical trials. When drug treatment 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.

It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy of elevation in dose, and periodically thereafter (e.g. semiannually). Patients who develop increased transaminase levels should be monitored with a second liver function tests until the abnormality returns to normal.

The drug should be used with caution in patients who consume substantial quantities of alcohol *and/or* have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of Simvastatin.

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.

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

DRUG INTERACTIONS:
Drug interactions with immunosuppressive drugs, itraconazole, gemfibrozil, niacin (Nicotinic Acid), erythromycin, digoxin, anticoagulants, and coumarin derivatives have been reported.

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) is contraindicated.

Other drug interac*tions*
Other Fibrates: The risk of myopathy is increased by gemfibrozil 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.

Fusidic Acid:
The risk of myopathy/rhabdomyolysis may be increased by concomitant administration of fusidic acid.

Amiodarone:
The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone with simvastatin.

Calcium channel blockers: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of verapamil, diltiazem, or amlodipine.

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. 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.

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

USE IN PREGNANCY AND LACTATION:
Pregnancy
Simvastatin should be administered to women of child bearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, Simvastatin should be discontinued and the patient should be apprised of the potential hazard to the foetus.

Lactation: It is not known weather simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants.

DOSAGE AND ADMINISTRATION:
The recommended starting dose is 5 to 10mg once a day in the evening. The recommended dosing range is 5 to 40 mg/day as a single dose in the evening. The maximum recommended dose is 40 mg/day. Doses should be individualized according to baseline LDL-C levels, the recommended goal of therapy and the patient's response.

Patients requiring reductions in LDL cholesterol of 20% or more to achieve their goal should be started on 10mg/day of Simvastatin.

A starting dose of 5mg should be considered for patients requiring smaller reductions and for the elderly. Adjustments of dosage should be made at intervals of 4 weeks or more. Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage if cholesterol level falls significantly below the targeted range.

Due to the increased risk of myopathy, including rhabdomyolysis, particularly during the first year of treatment, use of the 80-mg dose of simvastatin should be restricted to patients who have been taking simvastatin 80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity. Patients unable to achieve their LDL-C goal utilizing the 40-mg dose of simvastatin should not be titrated to the 80-mg dose, but should be placed on alternative LDL-C-lowering treatment(s) that provides greater LDL-C lowering.

Dosage on patients with Renal Insufficiency: Because simvastatin does not undergo significant renal excretion, modification of dosage should not be necessary in patients with mild to moderate renal insufficiency. However, caution should be exercised when simvastatin is administered to patients with sever renal insufficiency; such patients should be started at 5 mg/day and closely monitored.

OVERDOSAGE, SYMPTOMS AND ANTIDOTE:
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. Until further experience is obtained, no specific treatment of over dosage with Simvastatin and its metabolites in man is known at present.

PRESENTATION:
Simvastatin Tablets USP 10 mg (Simvas-10) Tablets packed in Alu-Alu blister pack of 10's (Box of 30's, Box of 50's and Box of 100's)
Simvastatin Tablets USP 20 mg (Simvas-20) Tablets packed in Alu-Alu blister pack of 10's (Box of 30's, Box of 50's and Box of 100's)
Not all presentations may be available locally.

STORAGE:
Store at or below 25°C. Keep all medicine away from reach of children.

DATE OF PUBLICATION:
November 2000

DATE OF REVISION:
July. 2016

Manufactured by:
MICRO LABS LIMITED
92, Sipcot Industrial Complex,
Hosur-635 126, INDIA.

Simvas-10: SIN 11951 P
Simvas-20: SIN 11950 P

EXG-ML01I-1290/A