SIVACOL 20 TABLET

COMPOSITION
Each tablet contains Simvastatin 20mg.

PRODUCT DESCRIPTION
A tan colored, oval shape, film coated tablet with score on one side.

PHARMACODYNAMICS
Simvastatin is a lipid-lowering drug which is synthetically derived from fermentation of Aspergillus terreus. While the parent compound is an inactive lactone, it is readily hydrolyzed in vivo to its corresponding β-hydroxyacid form, which is a potent inhibitor of 3-hydroxy-3 methylglutarylcoenzyme A (HMG-CoA) reductase. HMG-CoA reductase is the enzyme that catalyses the conversion of HMG-CoA to mevalonate, the rate-limiting step in the biosynthesis pathway for cholesterol in the body. As a result, the production of cholesterol is inhibited. However, inhibition of HMG-CoA is not complete, and simvastatin has been shown not to have any clinical effects on steroidogenesis.

Simvastatin has been shown to reduce total plasma cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), triglycerides (TG) and very low-density lipoprotein cholesterol (VLDL-C), and increasing high density lipoprotein cholesterol (HDL-C). Therapeutic effects are seen within 2 weeks and maximal effects within 4-6 weeks of oral administration.

PHARMACOKINETICS
About 85% of oral dose of simvastatin is absorbed. It undergoes extensive first-pass extraction in the liver, its primary site of action, and only a small amount of the drug reaches the systemic circulation. Simvastatin and its metabolites are excreted mainly by faeces, with lesser amounts in the urine. In plasma, the inhibitors (of HMG-CoA reductase activity) account for 14% and 28% (active and total inhibitors) of the AUC of total radioactivity after an oral dose of ^{14}C-simvastatin. The maximum plasma concentrations of inhibitors are achieved within 1-3 hours after oral administration.

INDICATIONS
In patients with coronary heart disease (CHD), simvastatin is indicated to:
- Reduce the risk of death
- Reduce the risk of coronary death and non-fatal myocardial infarction
- Reduce the risk for undergoing myocardial revascularization procedures (e.g. coronary artery bypass or angioplasty)
- Slow the progression of coronary atherosclerosis, including reducing the development of new occlusions and new total occlusions

In patients with hyperlipidemia, simvastatin is indicated:
- As an adjunct to dietary intervention to reduce elevated total-C, LDL-C, Apo B and TG, and to increase HDL-C in those with primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia and mixed hypercholesterolaemia when dietary modifications or other lipid-lowering measures are inadequate.

DOSAGE ANDADMINISTRATION

The dosage range for SIVACOL 20 TABLET 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 SIVACOL 20 TABLET 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 SIVACOL 20 TABLET and should continue this diet during treatment with SIVACOL 20 TABLET. 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 SIVACOL 20 TABLET. 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 SIVACOL 20 TABLET, 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). SIVACOL 20 TABLET 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 SIVACOL 20 TABLET, the dose of SIVACOL 20 TABLET should not exceed 40 mg/day (see PRECAUTIONS, Myopathy/Rhabdomyolysis and DRUG INTERACTIONS).

CONCOMITANT THERAPY

SIVACOL 20 TABLET is effective alone or in combination with bile acid sequestrants.

In patients taking SIVACOL 20 TABLET concomitantly with fibrates (other than gemfibrozil or fenofibrate), the dose of SIVACOL 20 TABLET should not exceed 10 mg/day. In patients taking amiodarone, verapamil, diltiazem, or products containing elbasvir or grazoprevir concomitantly with SIVACOL 20 TABLET, the dose of SIVACOL 20 TABLET should not exceed 20mg/day. In patients taking amlodipine concomitantly with SIVACOL 20 TABLET, the dose of SIVACOL 20 TABLET should not exceed 40 mg/day. (See PRECAUTIONS, Myopathy/Rhabdomyolysis and DRUG INTERACTIONS.)

DOSAGE IN RENAL INSUFFICIENCY

Because SIVACOL 20 TABLET 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 ACTION AND PHARMACOLOGY).

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 ACTION AND PHARMACOLOGY).

ROUTE OF ADMINISTRATION

Oral administration

CONTRAINDICATION

Simvastatin is contraindicated in the following conditions:

- Hypersensitivity to the drug or to any component of the product
- Active liver disease or persistent elevations of serum transaminases
- During pregnancy and lactation
- Concomitant administration of potent CYP3A4 inhibitors (e.g itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telitromycin and nefazodone)
- Concomitant administration of gemfibrozil, cyclosporine, or danazol

ADVERSE EFFECTS

Generally, side-effects of simvastatin are mild and transient, the most commonly reported being: abdominal pain, constipation, flatulence, asthenia, headache and rarely myopathy. Other side effects include: nausea, vomiting, skin rashes, and pruritus, dizziness, muscle cramps, pancreatitis, rarely rhabdomyolysis and hepatitis. Hypersensitivity reactions have also been reported rarely.

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.

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

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.

Musculoskeletal disorders
Frequency not known: Immune-mediated necrotizing myopathy.

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

Eye disorders
Frequency 'not known': ocular myasthenia.

WARNING AND PRECAUTIONS

Simvastatin should be used with caution in patients who have a past history of liver disease o who are alcoholics. Active liver diseases or unexplained elevations of serum transaminases are contraindications to use of simvastatin. Transient moderate elevations of serum transaminases during the initial period of treatment have been reported with simvastatin, and no discontinuation of therapy was required.

As with other HMG-CoA reductase inhibitors, simvastatin may cause myopathy, accompanied by muscle pain or weakness and grossly elevated creatine kinase (>10×the upper limit of normal, ULN). Rhabdomyolysis, with or without acute renal failure due to myoglobinuria, has also been reported on rare occasions.

The incidence and severity of myopathy are increased by concurrent administrations with gemfibrozil and other fibrates, and niacin (nicotinic acid) (>1g/day). Drugs such as cyclosporin, azole antifungals, the macrolide antibiotics and HIV protease inhibitors which inhibit the cytochrome P-450 isoform 3A4 (CYP3A4), the enzyme that metabolizes simvastatin and other HMG-CoA reductase inhibitors, may also increase the risk of myopathy.

The dose of simvastatin should not exceed 20mg daily in patients receiving concomitant medication with amiodarone or verapamil. The combined use of simvastatin at doses higher than 20mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy.

Measures to reduce the risk of myopathy

1. Patients should be told to inform their doctor if there is any unexplained muscle pain, tenderness or weakness. If such symptoms are also associated with increased creatine kinase levels >10×ULN, simvastatin therapy should be discontinued immediately. In patients who are susceptible to rhabdomyolysis (e.g. diabetes, pre-existing renal insufficiency), dosage increments should be done with caution. Treatment with simvastatin should be stopped a few days before elective major surgery and when any major acute medical or surgical conditions arise.
2. If combination therapy of simvastatin with fibrates, niacin or other interacting drugs must be instituted, extreme caution should be exercised. The patient should be monitored carefully for any signs and symptoms of muscle pain, tenderness or weakness, particularly during the first few months of therapy and when dosage increments are made. Creatine kinase levels should be monitored. In patients taking concomitant cyclosporin, fibrates or niacin, dosage of simvastatin should not exceed 10mg daily.
3. Simultaneous therapy with drugs that inhibit CYP3A4 should be avoided unless the potential benefits of combined therapy outweigh the potential risk.

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.

Myasthenia Gravis/ Ocular Myasthenia
In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia. SIVACOL 20 TABLET should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

Use in children
Safety and efficacy in children have not been established. Simvastatin is not recommended for use in children at this time.

Use in elderly
There is no evidence of increased frequency of adverse findings in elderly patients given simvastatin compared to the population as a whole.

PREGNANCY AND LACTATION

As cholesterol and other products of the cholesterol biosynthesis pathway are essential for fetal development, simvastatin and other HMG-CoA reductase inhibitors are contraindicated during pregnancy. It should be given to women of child-bearing age only when such patients are highly unlikely to conceive. Treatment with simvastatin should be discontinued immediately as soon as pregnancy is recognized.

It is not known if 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 in the nursing infant, nursing mothers should not breast-feed their babies when taking simvastatin.

DRUG INTERACTIONS

Contraindicated drugs
Potent inhibitors of CYP3A4: concomitant use with medicines labelled 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.

Concurrent use of fibrates may cause severe myositis and myoglobinuria

Other drugs
- Other fibrates: The dose of simvastatin should not exceed 10mg 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 risk 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.
- 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 20mg daily in patients receiving concomitant medication with amiodarone.

- Calcium channel blockers:
  - Verapamil or diltiazem: In clinical trial, patients on diltiazem treated concomitantly with simvastatin 80mg had an increased risk of myopathy. The dose of simvastatin should not exceed 20mg daily in patients receiving concomitant medication with verapamil or diltiazem.
  - Amlodipine: In a clinical trial, patients on amlodipine treated concomitantly with simvastatin 80mg had a slightly increased risk of myopathy. The dose of simvastatin should not exceed 40mg 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/daily. Cases of myopathy/ rhabdomyolysis have been observed with simvastatin co-administered with lipid- modifying doses (≥ 1g/daily).
- *Coumarin derivatives*: In patients on coumarin anticoagulants, prothrombin time should be closely monitored during initial period of simvastatin therapy, and when the dose of simvastatin is changed or discontinued.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

SIVACOL 20 TABLET has no or negligible influence on the ability to drive and use machines. However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported rarely in post-marketing experiences.

OVERDOSAGE AND TREATMENT

If overdosage occurs, the unabsorbed drug should be removed by induction of emesis or a gastric lavage. If overdosage occurs, there is no specific antidote and symptomatic measures should be given as appropriate. In reported cases of overdosage, no patients had specific symptoms and all recovered with no sequelae.

STORAGE

Store in a dry place below 30°C.
Protect from light.

PRESENTATION

Blister of 10 tablets, box of 3 or 10 strips.

PRODUCT REGISTRATION HOLDER AND MANUFACTURER:

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Lot 5030, Jalan Teratai,
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41050 Klang, Selangor, Malaysia.

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