

Pharmaniaga Simvastatin Tablet

DESCRIPTION

Pharmaniaga Simvastatin Tablet 10mg

Peach, oval-shaped, biconvex film coated tablet, with 'SIM 10' marking on one side and scored on the other.

Pharmaniaga Simvastatin Tablet 20mg

Brown, oval-shaped, biconvex, film coated tablet, plain on one side and scored on the other.

Pharmaniaga Simvastatin Tablet 40mg

Red, oblong, film coated tablet, embossed 'Pharmaniaga icon' on one side and scored on the other.

COMPOSITION

Each film-coated tablet contains:

Simvastatin 10mg, 20mg and 40mg.

PHARMACODYNAMICS

Simvastatin is a specific inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (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 simvastatin 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.

PHARMACOKINETICS

Simvastatin is absorbed from the gastrointestinal tract and must be hydrolysed to its active β -hydroxyacid form. Other active metabolites have been detected and several inactive metabolites are also formed. Simvastatin is a substrate for the cytochrome P450 isoenzyme CYP3A4 and undergoes extensive first-pass metabolism in the liver, its primary site of action. Less than 5 % of the oral dose has been reported to reach the circulation as active metabolites. Both simvastatin and its β -hydroxyacid metabolite are about 95 % bound to plasma proteins. Simvastatin is mainly excreted in the faeces via the bile as metabolites. About 10 to 15 % is recovered in the urine, mainly in inactive forms. The half-life of the active β -hydroxyacid metabolite is 1.9 hours.

INDICATIONS

Reductions in risk of coronary heart disease (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, simvastatin 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

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

Pediatric patients with heterozygous familial hypercholesterolemia

Simvastatin 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 simvastatin, 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.

CONTRAINDICATIONS

- Hypersensitivity to any component of this preparation.
- Active liver disease or unexplained persistent elevations of serum transaminases.
- Pregnancy and nursing.
- 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).

- Concomitant administration of gemfibrozil, cyclosporine, or danazol.

ADVERSE REACTIONS

Nervous system disorder:

Not known: myasthenia gravis

Eye disorder:

Not known: ocular myasthenia

Blood and lymphatic system disorders:

Rare: anaemia

Immune system disorders:

Very rare: anaphylaxis

Psychiatric disorders:

Very rare: insomnia

Not known: depression

Nervous system disorders:

Rare: headache, paresthesia, dizziness, peripheral neuropathy

Very rare: memory impairment

Respiratory, thoracic and mediastinal disorders:

Not known: interstitial lung disease

Gastrointestinal disorders:

Rare: constipation, abdominal pain, flatulence, dyspepsia, diarrhoea, nausea, vomiting, pancreatitis

Hepatobiliary disorders:

Rare: hepatitis/ jaundice

Very rare: fatal and non-fatal hepatic failure

Skin and subcutaneous tissue disorders:

Rare: rash, pruritus, alopecia

Musculoskeletal and connective tissue disorders:

Rare: myopathy (including myositis), rhabdomyolysis with or without acute renal failure, myalgia, muscle cramps

*Not known: tendinopathy, sometimes complicated by rupture; immune-mediated necrotizing myopathy (IMNM)***

****** There have been very rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, 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.

Reproductive system and breast disorders:

Not known: erectile dysfunction

General disorders and administration site conditions:

Rare: asthenia

An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features:

angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, ESR increased, arthritis and arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea and malaise.

Investigations:

Rare: increases in serum transaminases (alanine aminotransferase, aspartate aminotransferase, γ -glutamyl transpeptidase), elevated alkaline phosphatase; increase in serum CK levels.

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

The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.

There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use, including simvastatin. 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).

The following additional adverse events have been reported with some statins:

- Sleep disturbances, including nightmares
- Sexual dysfunction
- Diabetes mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose $\geq$ 5.6 mmol/L, BMI > 30 kg/m², raised triglycerides, history of hypertension).

Paediatric population

The long-term effects on physical, intellectual, and sexual maturation are unknown. No sufficient data are currently available.

WARNINGS AND 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 IOX 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

level of HMG-CoA reductase in 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. 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.

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 simvastatin 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.

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.

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.

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 inhibitor 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.

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

Other drugs

- **Fusidic acid:** Patients on fusidic acid treated concomitantly with simvastatin may have an increased risk of myopathy/rhabdomyolysis. 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 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.

- **Amiodarone:** The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone.

• **Calcium channel blockers**

- Verapamil or diltiazem:** The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with verapamil or diltiazem.

- Amlodipine:** 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.

- **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.

- **Daptomycin:** Reports of myopathy and/or rhabdomyolysis have been observed with HMGCoA 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 simvastatin temporarily in patients taking daptomycin.

- **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.

- **Niacin (≥ 1 g/day):** The dose of simvastatin should not exceed 40mg daily in patients receiving concomitant medication with niacin (nicotinic acid) ≥ 1 g/day. Cases of myopathy/rhabdomyolysis have been observed with simvastatin co-administered with lipid-modifying doses (≥ 1 g/day) of niacin.

Myasthenia Gravis/Ocular Myasthenia

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

Hepatic effects

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.

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 all ALT may emanate from muscles, therefore ALT rising with CK may indicate myopathy.

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 simvastatin, promptly interrupt therapy. If an alternate etiology is not found, do not restart simvastatin.

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.

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.

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 cycle length in girls. Adolescent females should be counseled on appropriate contraceptive methods while on simvastatin therapy. Simvastatin has not been studied in patients younger than 10 years of age, nor in premenarchal 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.

Diabetes mellitus

Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore

should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI > 30 kg/m², raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Interstitial lung disease

Cases of interstitial lung disease have been reported with some statins, including simvastatin, especially with long term therapy. Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Excipient

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

EFFECT ON ABILITY TO DRIVE AND USE MACHINE

Simvastatin 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.

PREGNANCY AND LACTATION

Use in pregnancy:

Simvastatin 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.

Although there is no evidence that the incidence of congenital anomalies in offspring of patients taking simvastatin or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with simvastatin 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, simvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment With simvastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant.

Use in lactation:

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 simvastatin should not breast-feed their infants.

DRUG INTERACTIONS

Multiple mechanisms may contribute to potential interactions with HMG Co-A reductase inhibitors. 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.

Contraindicated drugs

Concomitant use of the following drugs is contraindicated:

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.

Other drug interactions

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.

Lomitapide: The risk of myopathy/rhabdomyolysis may be increased by concomitant administration of lomitapide.

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): The dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with 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.

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.

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.

Daptomycin: The risk of myopathy and/or rhabdomyolysis may be increased by coadministration of HMG-CoA reductase inhibitors and daptomycin.

Ciclosporin: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ciclosporin with simvastatin; therefore, use with ciclosporin is contraindicated. Although the mechanism is not fully understood, ciclosporin has been shown to increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4 and/or OATP1B1.

Rifampicin: Because rifampicin is a potent CYP3A4 inducer, patients undertaking long-term rifampicin therapy (e.g. treatment of tuberculosis) may experience loss of efficacy of simvastatin. In a pharmacokinetic study in normal volunteers, the area under the plasma concentration curve (AUC) for simvastatin acid was decreased by 93% with concomitant administration of rifampicin.

Oral anticoagulants

Very rare cases of elevated INR have been reported. 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.

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.

DOSAGE AND ADMINISTRATION

The dosage range for simvastatin 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 80mg dose of simvastatin 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. 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 simvastatin 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 simvastatin and should continue on this diet during treatment with simvastatin. 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 simvastatin. Adjustments of dosage, if required, should be made as specified above.

Patient with homozygous familial hypercholesterolemia

The recommended dosage for patients with homozygous familial hypercholesterolemia is simvastatin 40 mg/day in the evening. The 80-mg dose is only recommended when the benefits are expected to outweigh the potential risks. Simvastatin should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or It such treatments are unavailable. In patients taking lomitapide concomitantly with simvastatin, the dose of simvastatin should not exceed 40 mg/day.

Concomitant therapy

Simvastatin is effective alone or in combination with bile acid sequestrants. In patients taking simvastatin concomitantly with fibrates (other than gemfibrozil or fenofibrate), the dose of simvastatin should not exceed 10 mg/day. In patients taking amiodarone, verapamil or diltiazem concomitantly with simvastatin, the dose of simvastatin should not exceed 20mg/day. In patients taking amlodipine or lipid-lowering dose of niacin (≥ 1g/day) concomitantly with simvastatin, the dose of simvastatin should not exceed 40 mg/day.

Dosage in 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 <30 mL/min), dosages above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously.

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.

Mode of Administration

Oral

OVERDOSAGE

A few cases of overdosage have been reported. The maximum dose taken was 3.6g. All patients recovered without sequelae. General measures should be adopted.

STORAGE CONDITION

Store below 30°C. Protect from light.

SHELF LIFE

Product should not be used beyond the expiry date imprinted on the product packaging.

PRESENTATION

In blisters of 10, 30, 100, 120 and 500 tablets.

Date of revision: 15th October 2025

PRODUCT MANUFACTURER:	REGISTRATION	HOLDER/
Pharmaniaga (198001006232)	Manufacturing	Berhad
No. 11A, Jalan P/1, Kawasan Perusahaan Bangi, 43650 Bandar Baru Bangi, Selangor Darul Ehsan, Malaysia.		
PRP0387.13/ PRP0388.13/ PRP0385.13 151025		