SimvaHEXAL® 10 mg & 20 mg Film-Coated Tablets

CONTENT

Each **SimvaHEXAL® 10 mg** and **SimvaHEXAL® 20 mg** film-coated tablets contains 10 mg and 20 mg Simvastatin respectively.

DESCRIPTION

SimvaHEXAL® 10 mg film-coated tablet: Pale pink coated, oval, scored, convex tablet coded SIM 10 on one side.
SimvaHEXAL® 20 mg film-coated tablet: Orange coated, oval, scored, convex tablet coded SIM 20 on one side.
Each tablet can be divided into equal halves.

PHARMACODYNAMICS

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolysed in the liver to the corresponding active beta-hydroxyacid form which has a potent activity in inhibiting HMG-CoA reductase (3-hydroxy-3-methylglutaryl-CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.
Simvastatin has been shown to reduce both normal and elevated low-density lipoprotein cholesterol (LDL-C) concentrations. LDL is formed from very-low-density lipoprotein (VLDL) and is catabolised predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of simvastatin may involve both reduction of VLDL-cholesterol (VLDL-C) concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL-C. Apolipoprotein B also falls substantially during treatment with simvastatin. In addition, simvastatin moderately increases high-density lipoprotein cholesterol (HDL-C) and reduces plasma triglyceride (TG). As a result of these changes the ratios of total- to HDL-C and LDL- to HDL-C are reduced.

PHARMACOKINETICS

Simvastatin is an inactive lactone which is readily hydrolysed *in vivo* to the corresponding beta-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Hydrolysis takes place mainly in the liver; the rate of hydrolysis in human plasma is very slow. The pharmacokinetic properties have been evaluated in adults. Pharmacokinetic data in children and adolescents are not available.

Absorption: In man, simvastatin is well absorbed and undergoes extensive hepatic first-pass extraction. The extraction in the liver is dependent on the hepatic blood flow. The liver is the primary site of action of the active form. The availability of the beta-hydroxyacid to the systemic circulation following an oral dose of simvastatin was found to be less than 5% of the dose. Maximum plasma concentration of active inhibitors is reached approximately 1-2 hours after administration of simvastatin. Concomitant food intake does not affect the absorption. The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of medicinal product occurred after multiple dosing.

Distribution: The protein binding of simvastatin and its active metabolites is > 95%.

Elimination: Simvastatin is a substrate of CYP3A4. The major metabolites of simvastatin present in human plasma are the beta-hydroxyacid and four additional active metabolites. Following an oral dose of radioactive simvastatin to man, 13% of the radioactivity was excreted in the urine and 60% in the faeces within 96 hours. The amount recovered in the faeces represents absorbed medicinal product equivalents excreted in bile as well as unabsorbed medicinal product. Following an intravenous injection of the beta-hydroxyacid metabolite, its half-life averaged 1.9 hours. An average of only 0.3% of the IV dose was excreted in urine as inhibitors. Simvastatin acid is taken up actively into the hepatocytes by the transporter OATP1B1. Simvastatin is a substrate of the efflux transporter BCRP.

Special Populations

SLCO1B1 polymorphism

Carriers of the SLCO1B1 gene c.521T>C allele have lower OATP1B1 activity. The mean exposure (AUC) of the main active metabolite, simvastatin acid is 120% in heterozygote carriers (CT) of the C allele and 221% in homozygote (CC) carriers relative to that of patients who have the most common genotype (TT). The C allele has a frequency of 18% in the European population. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of simvastatin acid, which may lead to an increased risk of rhabdomyolysis (see WARNINGS & PRECAUTIONS).

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, **SimvaHEXAL®** 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.

Hyperlipidaemia

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

Paediatric Patients with Heterozygous Familial Hypercholesterolaemia (HeFH)

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 hypercholesterolaemia (HeFH).

General Recommendations

Prior to initiating therapy with simvastatin, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.

RECOMMENDED DOSAGE

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 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. 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 hyperlipidaemia), i.e., 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 Hyperlipidaemia (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 40 mg/day given as single dose in the evening. Patients with mild to moderate hypercholesterolaemia can be treated with a starting dose of 10 mg of simvastatin. Adjustments of dosage, if required, should be made as specified above.

Patients with Homozygous Familial Hypercholesterolaemia (HoFH)

The recommended dosage for patients with homozygous familial hypercholesterolaemia 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 if 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, diltiazem, or products containing elbasvir or grazoprevir concomitantly with simvastatin, the dose of simvastatin should not exceed 20 mg/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 (see WARNINGS & PRECAUTIONS, DRUG INTERACTIONS).

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 Paediatric Patients (10-17 years of age) with Heterozygous Familial Hypercholesterolaemia

The recommended usual starting dose is 10 mg once a day in the evening. The recommended dosing range is 10-40 mg/day; the maximum recommended dose is 40 mg/day. Doses should be individualized according to the recommended goal of therapy.

MODE OF ADMINISTRATION
Oral administration

CONTRAINDICATIONS
• Hypersensitivity to simvastatin or to any of the excipients.
• Active liver disease or unexplained persistent elevations of serum transaminases.
• Pregnancy and lactation.
• 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, ciclosporin or danazol.
• In patients with HoFH, concomitant administration of lomitapide with doses > 40 mg simvastatin.

WARNINGS & 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 ten times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and very rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma (i.e., elevated simvastatin and simvastatin acid plasma levels), which may be due, in part, to interacting medicinal products 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 (see below Measures to reduce the risk of myopathy caused by medicinal product interactions and sections RECOMMENDED DOSAGE, CONTRAINDICATIONS, DRUG INTERACTIONS).

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

Reduced function of transport proteins
Reduced function of hepatic OATP transport proteins can increase the systemic exposure of simvastatin acid and increase the risk of myopathy and rhabdomyolysis. Reduced function can occur as the result of inhibition by interacting medicines (e.g. ciclosporin) or in patients who are carriers of the SLCO1B1 c.521T>C genotype. Patients carrying the SLCO1B1 gene allele (c.521T>C) coding for a less active OATP1B1 protein have an increased systemic exposure of simvastatin acid and increased risk of myopathy. The risk of high dose (80 mg) simvastatin related myopathy is about 1% in general, without genetic testing.

Creatine Kinase measurement
Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at baseline (> 5X ULN), levels should be re-measured within 5 to 7 days later to confirm the results.

Before the treatment
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.
Caution should be exercised in patients with predisposing factors for rhabdomyolysis. In order to establish a reference baseline value, a CK level should be measured before starting a treatment in the following situations:
• Elderly (age ≥ 65 years)
• Female gender
• Renal impairment
• Uncontrolled hypothyroidism
• Personal or familial history of hereditary muscular disorders
• Previous history of muscular toxicity with a statin or fibrate
• Alcohol abuse

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended. If a patient has previously experienced a muscle disorder on a fibrate or a statin, treatment with a different member of the class should only be initiated with caution. If CK levels are significantly elevated at baseline (> 5X ULN), treatment should not be started.

Whilst on treatment
If muscle pain, weakness or cramps occur whilst a patient is receiving treatment with a statin, their CK levels should be measured. If these levels are found, in the absence of strenuous exercise, to be significantly elevated (> 5X ULN), treatment should be stopped. If muscular symptoms are severe and cause daily discomfort, even if CK levels are < 5X ULN, treatment discontinuation may be considered. If myopathy is suspected for any other reason, treatment should be discontinued.

There have been very rare reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterised by:
• Persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment;
• Muscle biopsy showing necrotising myopathy without significant inflammation;
• Improvement with immunosuppressive agents.

If symptoms resolve and CK levels return to normal, then re-introduction of the statin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.

A higher rate of myopathy has been observed in patients titrated to the 80 mg dose. Periodic CK measurements are recommended as they may be useful to identify subclinical cases of myopathy. However, 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.

Measures to reduce the risk of myopathy caused by medicinal product interactions (see also DRUG INTERACTIONS)
The risk of myopathy and rhabdomyolysis is significantly increased by concomitant use of simvastatin with potent inhibitors of CYP3A4 (such as itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, nefazodone, medicinal products containing cobicistat), as well as gemfibrozil, ciclosporin and danazol. Use of these medicinal products is contraindicated. If short-term treatment with potent CYP3A4 inhibitors is unavoidable, therapy with simvastatin should be suspended during the course of treatment.

The risk of myopathy and rhabdomyolysis is also increased by concomitant use of amiodarone, amlodipine, verapamil or diltiazem with certain doses of simvastatin. The risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of fusidic acid with statins. For patients with HoFH, this risk may be increased by concomitant use of lomitapide with simvastatin. Moreover, caution should be exercised when combining simvastatin with certain other less potent CYP3A4 inhibitors: fluconazole, verapamil, diltiazem. Concomitant intake of grapefruit juice and simvastatin should be avoided.

The use of simvastatin with gemfibrozil is contraindicated. Due to the increased risk of myopathy and rhabdomyolysis, the dose of simvastatin should not exceed 10 mg daily in patients taking simvastatin with other fibrates (except fenofibrate). Caution should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone.

Patients on fusidic acid treated concomitantly with simvastatin may have an increased risk of myopathy and rhabdomyolysis. Co-administration with fusidic acid is not recommended. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Statin therapy may be re-introduced seven days after the last dose of fusidic acid. 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 and under close medical supervision.

The combined use of simvastatin at doses higher than 20 mg daily with amiodarone, verapamil or diltiazem should be avoided. The dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with amlodipine. In patients with HoFH, the combined use of simvastatin at doses higher than 40 mg daily with lomitapide must be avoided.

Patients taking other medicines labelled as having a moderate inhibitory effect on CYP3A4 concomitantly with simvastatin, particularly higher simvastatin doses, may have an increased risk of myopathy. When co-administering simvastatin with a moderate inhibitor of CYP3A4, a dose adjustment of simvastatin may be necessary.

Simvastatin is a substrate of the Breast Cancer Resistant Protein (BCRP) efflux transporter. 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 should be considered depending on the prescribed dose. 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 medicinal products containing elbasvir or grazoprevir.

Rare cases of myopathy/rhabdomyolysis have been associated with concomitant administration of HMG-CoA reductase inhibitors and lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid), either of which can cause myopathy when given alone. Therefore, physicians contemplating combined therapy with simvastatin and lipid-modifying doses (≥ 1 g/day) of niacin (nicotinic acid) or products containing niacin should carefully 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 when the dose of either medicinal product is increased. While the only Asian population assessed in the clinical trial was Chinese, because the incidence of myopathy is higher in Chinese than in non-Chinese patients, co-administration of simvastatin with lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid) is not recommended in Asian patients. Acipimox is structurally related to niacin. Although acipimox was not studied, the risk for muscle related toxic effects may be similar to niacin.

Reports of myopathy and/or rhabdomyolysis have been observed with HMG-CoA reductase inhibitors co-administered 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.

Hepatic effects
In clinical studies, persistent increases (to > 3X ULN) in serum transaminases have occurred in a few adult patients who received simvastatin. When simvastatin was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pre-treatment levels.

It is recommended that liver function tests 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. semi-annually) 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, simvastatin should be discontinued. Note that ALT may emanate from muscle, 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 hyperbilirubinaemia or jaundice occurs during treatment with simvastatin, promptly interrupt therapy. If an alternate aetiology 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 (<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.

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/m^2, 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.

Paediatric population
Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolaemia have been evaluated in a controlled clinical trial in adolescent boys Tanner Stage II and above 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 counselled on appropriate contraceptive methods while on simvastatin therapy. In patients aged < 18 years, efficacy and safety have not been studied for treatment periods > 48 weeks' duration and long-term effects on physical, intellectual, and sexual maturation are unknown. Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-pubertal children and pre-menarchal girls.

Elderly
For patients over the age of 65 years who received simvastatin in controlled clinical studies, efficacy, as assessed by reduction in total- and LDL-cholesterol levels, 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.

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.

Effects on ability to drive and use machines
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.

DRUG INTERACTIONS
Multiple mechanisms may contribute to potential interactions with HMG-CoA 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.

Consult the prescribing information of all concomitantly used drugs to obtain further information about their potential interactions with simvastatin and/or the potential for enzyme or transporter alterations and possible adjustments to dose and regimens. Interaction studies have only been performed in adults.

Prescribing recommendations for interacting agents are summarised in the table below (further details are provided in the text; see also RECOMMENDED DOSAGE, CONTRAINDICATIONS, WARNINGS & PRECAUTIONS).

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis	
Interacting Agents	**Prescribing Recommendations**
Potent CYP3A4 inhibitors, e.g.: Itraconazole, Ketoconazole, Posaconazole, Voriconazole, Erythromycin, Clarithromycin, Telithromycin, HIV protease inhibitors (e.g. nelfinavir), Boceprevir, Telaprevir, Nefazodone, Ciclosporin, Danazol, Gemfibrozil, Cobicistat	Contraindicated with simvastatin
Other fibrates (except fenofibrate)	Do not exceed 10 mg simvastatin daily

Fusidic acid	Not recommended with simvastatin
Niacin (nicotinic acid) (≥ 1g/day)	For Asian patients, not recommended with simvastatin
Amiodarone, Verapamil, Diltiazem, Elbasvir, Grazoprevir	Do not exceed 20 mg simvastatin daily
Amlodipine	Do not exceed 40 mg simvastatin daily
Lomitapide	For patients with HoFH, do not exceed 40 mg simvastatin daily
Daptomycin	It should be considered to temporarily suspend simvastatin in patients taking daptomycin unless the benefits of concomitant administration outweigh the risk
Grapefruit juice	Avoid grapefruit juice when taking simvastatin

Contraindicated Drugs
Concomitant use of simvastatin with the following medicines is contraindicated:
• **Potent inhibitors of CYP3A4**: Simvastatin is metabolised by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolised by CYP3A4. Potent inhibitors of CYP3A4 increase the risk of myopathy by reducing the elimination of simvastatin. 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, nefazodone and medicinal products containing cobicistat) is contraindicated. If treatment with potent CYP3A4 inhibitors is unavoidable, therapy with simvastatin should be suspended during the course of treatment.

• **Gemfibrozil**, **ciclosporin** 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 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.

• **Fusidic acid:** The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamics or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. Co-administration of this combination may cause increased plasma concentrations of both agents. If treatment with systemic fusidic acid is necessary, simvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment.

• **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 20 mg 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.

• **Fluconazole:** Rare cases of rhabdomyolysis associated with concomitant administration of simvastatin and fluconazole have been reported.

• **Lomitapide:** The risk of myopathy and rhabdomyolysis may be increased by concomitant administration of lomitapide with simvastatin. Therefore, in patients with HoFH, the dose of simvastatin must not exceed 40 mg daily in patients receiving concomitant medication with lomitapide.

• **Moderate inhibitors of CYP3A4**: Patients taking other medicines labelled as having a moderate inhibitory effect on CYP3A4 concomitantly with simvastatin, particularly higher simvastatin doses, may have an increased risk of myopathy.

• **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)**: Concomitant administration of medicinal 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 co-administering simvastatin with an inhibitor of BCRP, a dose adjustment of simvastatin may be necessary.

• **Niacin (nicotinic acid) (≥ 1g/day)**: The dose of simvastatin should not exceed 40 mg 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 (≥ 1 g/day) of niacin.

• **Ticagrelor**: Co-administration of ticagrelor with doses of simvastatin exceeding 40 mg daily could cause adverse reactions of simvastatin and should be weighed against potential benefits. There was no effect of simvastatin on ticagrelor plasma levels. The concomitant use of ticagrelor with doses of simvastatin greater than 40 mg is not recommended.

• **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.

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

• **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.

• **Coumarin derivatives:** 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.

• **Grapefruit juice**: Grapefruit juice inhibits cytochrome P450 3A4. Intake of grapefruit juice during treatment with simvastatin should therefore be avoided.

PREGNANCY & LACTATION
Pregnancy
Simvastatin is contraindicated during pregnancy. Safety in pregnant women has not been established. 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 foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia. For these reasons, simvastatin must not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with simvastatin must be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant.

Lactation
It is not known whether simvastatin or its metabolites are excreted in human milk. Because many medicinal products are excreted in human milk and because of the potential for serious adverse reactions, women taking simvastatin must not breastfeed their infants.

SIDE EFFECTS
The frequencies of adverse events are ranked accordingly.
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, paraesthesia, dizziness, peripheral neuropathy
Very rare: Memory impairment
Not known: Myasthenia gravis

Eye disorders
Rare: Vision blurred, visual impairment
Not known: Ocular myasthenia

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
Very rare: Lichenoid drug eruptions

Musculoskeletal and connective tissue disorders
Rare: Myopathy (including myositis), rhabdomyolysis with or without acute renal failure, myalgia, muscle cramps
Very rare: Muscle rupture
Not known: Tendinopathy, sometimes complicated by rupture; immune-mediated necrotising myopathy (IMNM)*
*There have been very rare reports of immune-mediated necrotising myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is clinically characterised by: persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotising myopathy without significant inflammation; improvement with immunosuppressive agents.

Reproductive system and breast disorders
Very rare: Gynaecomastia
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: anaphylaxis, angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, ESR increased, arthritis, arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea and malaise.

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 3 weeks).

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.

Increases in HbA1c and fasting blood glucose have been reported with statins. The risk of hyperglycaemia, however, is outweighed by the reduction in vascular risk with statins.

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 ≥ 5.6 mmol/L, BMI > 30 kg/m^2, raised triglycerides, history of hypertension).

SYMPTOMS AND TREATMENT OF OVERDOSE
To date, a few cases of overdose have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae. There is no specific treatment in the event of overdose. In this case, symptomatic and supportive measures should be adopted.

PRESENTATION
Blister pack of 7 tablets. Box of 28, 49, 98 film-coated tablets.
Blister pack of 10 tablets. Box of 10, 20, 30, 40, 50, and 100 film-coated tablets.
Shelf life: Please refer to the outer box label.

Do not store above 30°C.
Keep blisters in the outer carton to protect from light.

Keep the medicines out of reach of children
Jauhi daripada kanak-kanak

Manufactured for:
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Holzkirchen, Germany.

Bulk manufacturer:
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Ilaclari Sanayi ve Ticaret A.S.
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