Simvastatin

Vidastat®

20 mg Film-coated Tablet

40 mg Film-coated Tablet

Antihyperlipidemic Agent

℞

FORMULATION

20mg: Each film-coated tablet contains 20mg of Simvastatin

40mg: Each film-coated tablet contains 40mg of Simvastatin

PHARMACEUTICAL FORM

20mg: an orange, coated, oval, scored, convex tablet with code "SIM 20" on one side

40mg: a pink, coated, oval, scored, convex tablet with code "SIM 40" on one side

CLINICAL PARTICULARS

Indications

Hypercholesterolaemia

Treatment of primary hypercholesterolaemia or mixed dyslipidaemia as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Treatment of homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

Cardiovascular prevention

Reduction of cardiovascular mortality and morbidity in patients with manifest atherosclerotic cardiovascular disease or diabetes mellitus, with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors and other cardioprotective therapy (see Pharmacodynamic properties).

Dosage and administration

Dose directions

The dose range is 5-80 mg/day given orally as a single dose in the evening. Adjustments of dose, 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 with severe hypercholesterolaemia and 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 (see Special warnings and precautions for use and Pharmacodynamic properties).

Hypercholesterolaemia

The patient should be placed on a standard cholesterol-lowering diet, and should continue on this diet during treatment with simvastatin. The usual starting dose is 10-20 mg/day given as a single dose in the evening. Patients who require a large reduction in LDL-C (more than 45%) may be started at 20-40 mg/day given as a single dose in the evening. Adjustments of dose, if required, should be made as specified above.

Homozygous familial hypercholesterolaemia

Based on the results of a controlled clinical study, the recommended starting dose is simvastatin 40 mg/day in the evening. 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.

Cardiovascular prevention

The usual dose of simvastatin is 20 to 40 mg/day given as a single dose in the evening in patients at high risk of coronary heart disease (CHD, with or without hyperlipidaemia). Drug therapy can be initiated simultaneously with diet and exercise. Adjustments of dose, if required, should be made as specified above.

Concomitant therapy

Simvastatin is effective alone or in combination with bile acid sequestrants. Dosing should occur either >2 hours before or >4 hours after administration of a bile acid sequestrant.

In patients taking simvastatin concomitantly with fibrates, other than gemfibrozil (see Contraindications) or fenofibrate, the dose of simvastatin should not exceed 10 mg/day. In patients taking amiodarone, amiodipine, verapamil, or diltiazem concomitantly with simvastatin, the dose of simvastatin should not exceed 20 mg/day (see Special warnings and precautions for use and Interaction with other medicinal products and other forms of interaction).

Dose in renal insufficiency

No modification of dose should be necessary in patients with moderate renal insufficiency.

In patients with severe renal insufficiency (creatinine clearance <30 mL/min), doses above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously.

Use in the elderly

No dose adjustment is necessary.

Paediatric population (10-17 years of age)

For children and adolescents (boys Tanner Stage II and above and girls who are at least one year post-menarche, 10-17 years of age) with heterozygous familial hypercholesterolaemia, the recommended usual starting dose is 10 mg once a day in the evening. Children and adolescents should be placed on a standard cholesterol-lowering diet before simvastatin treatment initiation; this diet should be continued during simvastatin treatment.

The recommended dosing range is 10-40 mg/day; the maximum recommended dose is 40 mg/day. Doses should be individualised according to the recommended goal of therapy as recommended by the paediatric treatment recommendations (see Special warnings and precautions for use and Pharmacodynamic properties). Adjustments should be made at intervals of 4 weeks or more.

The experience of simvastatin in pre-pubertal children is limited.

Contraindications

- Hypersensitivity to simvastatin or to any of the excipients
- Active liver disease or unexplained persistent elevations of serum transaminases
- Pregnancy and lactation (see Pregnancy and lactation)
- Concomitant administration of potent CYP3A4 inhibitors (agents that increase AUC approximately 5-fold or greater) (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone and medicinal products containing cobicistat) (see Special warnings and precautions for use and Pharmacodynamic properties). Adjustments should be made at intervals of 4 weeks or more.

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Contraindications

- Hypersensitivity to simvastatin or to any of the excipients
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- Concomitant administration of potent CYP3A4 inhibitors (agents that increase AUC approximately 5-fold or greater) (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone and medicinal products containing cobicistat) (see Special warnings and precautions for use and Interaction with other medicinal products and other forms of interaction)
- Concomitant administration of gemfibrozil, ciclosporin, or danazol (see Special warnings and precautions for use and Interaction with other medicinal products and other forms of interaction)
- In patients with HoFH, concomitant administration of lomitapide with doses >40 mg simvastatin (see Dosage and administration, Special warnings and precautions for use, and Interaction with other medicinal products and other forms of interaction).

Special warnings and precautions for use

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.

As with other HMG-CoA reductase inhibitors, 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% (see Undesirable effects and Pharmacodynamic properties).

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 with severe hypercholesterolemia and 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 Dosage and administration, Contraindications, and Interaction with other medicinal products and other forms of interaction).

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 = 7,367) compared with 0.24 % for Chinese patients (n = 5,468). 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.

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. Based on the results of the SEARCH trial, homozygote C allele carriers (also called CC) treated with 80 mg have a 15% risk of myopathy within one year, while the risk in heterozygote C allele carriers (CT) is 1.5%. The corresponding risk is 0.3% in patients having the most common genotype (TT) (see Pharmacokinetic properties). Where available, genotyping for the presence of the C allele should be considered as part of the benefit-risk assessment prior to prescribing 80 mg simvastatin for individual patients and high doses avoided in those found to carry the CC genotype. However, absence of this gene upon genotyping does not exclude that myopathy can still occur.

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 (>5 x 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.

Caution should be exercised in patients with pre-disposing 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 (>5 x 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 (>5 x ULN), treatment should be stopped. If muscular symptoms are severe and cause daily discomfort, even if CK levels are <5 x 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 (see Undesirable effects).

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 (see Pharmacodynamic properties). 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.

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 Interaction with other medicinal products and other forms of interaction)

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. Concomitant administration of itraconazole resulted in a more than 10-fold increase in exposure to simvastatin acid (the active beta-hydroxyacid metabolite). Telithromycin caused an 11-fold increase in exposure to simvastatin acid.

Combination with itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone and medicinal products containing cobicistat is contraindicated, see Contraindications and Interaction with other medicinal products and other forms of interaction). If treatment with potent CYP3A4 inhibitors (agents that increase AUC approximately 5-fold or greater) is unavoidable, therapy with simvastatin must be suspended (and use of an alternative statin considered) during the course of treatment. Moreover, caution should be exercised when combining simvastatin with certain other less potent CYP3A4 inhibitors: fluconazole, verapamil, or diltiazem (see Dosage and administration and Special warnings and precautions for use).

Fluconazole

Rare cases of rhabdomyolysis associated with concomitant administration of simvastatin and fluconazole have been reported (see Special warnings and precautions for use).

Ciclosporin

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ciclosporin with simvastatin; therefore, use with ciclosporin is contraindicated (see Contraindications and Special warnings and precautions for use).

Although the mechanism is not fully understood, ciclosporin has been shown to increase the AUC of HMG-CoA reductase inhibitors. The increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4 and/or OATP1B1.

Danazol

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with simvastatin; therefore, use with danazol is contraindicated. (see Contraindications and Special warnings and precautions for use).

Gemfibrozil

Gemfibrozil increases the AUC of simvastatin acid by 1.9-fold, possibly due to inhibition of the glucuronidation pathway and/or OATP1B1 (see Contraindications and Special warnings and precautions for use). Concomitant administration with gemfibrozil is contraindicated.

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 pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with systemic fusidic acid is necessary, simvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment **(see also Special warnings and precautions for use)**.

Amiodarone

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone with simvastatin (see Special warnings and precautions for use). In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone. Therefore, the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone.

Calcium channel blockers

• *Verapamil*

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of verapamil with simvastatin 40 mg or 80 mg (see Special warnings and precautions for use). In a pharmacokinetic study, concomitant administration with verapamil resulted in a 2.3-fold increase in exposure of simvastatin acid, presumably due, in part, to inhibition of CYP3A4. Therefore, the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with verapamil.

• *Diltiazem*

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of diltiazem with simvastatin 80 mg (see Special warnings and precautions for use). In a pharmacokinetic study, concomitant administration of diltiazem caused a 2.7-fold increase in exposure of simvastatin acid, presumably due to inhibition of CYP3A4. Therefore, the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with diltiazem.

• *Amlodipine*

Patients on amlodipine treated concomitantly with simvastatin have an increased risk of myopathy. In a pharmacokinetic study, concomitant administration of amlodipine caused a 1.6-fold increase in exposure of simvastatin acid. Therefore, the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amlodipine.

Lomitapide

The risk of myopathy and rhabdomyolysis may be increased by concomitant administration of lomitapide with simvastatin (see Contraindications and Special warnings and precautions for use). 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 (see Special warnings and precautions for use).

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 (see Contraindications and Special warnings and precautions for use).

Niacin (nicotinic acid)

Rare cases of myopathy/rhabdomyolysis have been associated with simvastatin co-administered with lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid). In a pharmacokinetic study, the co-administration of a single dose of nicotinic acid prolonged-release 2 g with simvastatin 20 mg resulted in a modest increase in the AUC of simvastatin and simvastatin acid and in the C_{max} of simvastatin acid plasma concentrations.

Grapefruit juice

Grapefruit juice inhibits cytochrome P450 3A4. Concomitant intake of large quantities (over 1 L daily) of grapefruit juice and simvastatin resulted in a 7-fold increase in exposure to simvastatin acid. Intake of 240 mL of grapefruit juice in the morning and simvastatin in the evening also resulted in a 1.9-fold increase. Intake of grapefruit juice during treatment with simvastatin should therefore be avoided.

Colchicine

There have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and simvastatin in patients with renal impairment. Close clinical monitoring of such patients taking this combination is advised.

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.

Effects of simvastatin on the pharmacokinetics of other medicinal products

Simvastatin does not have an inhibitory effect on cytochrome P450 3A4. Therefore, simvastatin is not expected to affect plasma concentrations of substances metabolised via cytochrome P450 3A4.

Pharmacodynamic interactions

Interactions with lipid-lowering medicinal products that can cause myopathy when given alone

The risk of myopathy, including rhabdomyolysis, is increased during concomitant administration with fibrates. Additionally, there is a pharmacokinetic interaction with gemfibrozil resulting in increased simvastatin plasma levels (see below pharmacokinetic interactions, Contraindications, and Special warnings and precautions for use). 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. Adequate pharmacovigilance and pharmacokinetic data are not available for other fibrates. Rare cases of myopathy/rhabdomyolysis have been associated with simvastatin co-administered with lipid-modifying doses (≥1 g/day) of niacin (see Special warnings and precautions for use).

Pharmacokinetic interactions

Prescribing recommendations for interacting agents are summarised in the table below (further details are provided in the text; see also Dosage and administration, Contraindications and Special warnings and precautions for use).

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 Cobicistat Ciclosporin Danazol Gemfibrozil	Contraindicated with simvastatin
Other fibrates (except fenofibrate)	Do not exceed 10 mg simvastatin daily
Fusidic acid	Is not recommended with simvastatin
Niacin (nicotinic acid) (≥1g/day)	For Asian patients, not recommended with simvastatin
Amiodarone Amlodipine Verapamil Diltiazem	Do not exceed 20 mg simvastatin daily
Lomitapide	For patients with HoFH, do not exceed 40 mg simvastatin daily
Grapefruit juice	Avoid grapefruit juice when taking simvastatin

Effects of other medicinal products on simvastatin

Interactions involving inhibitors of CYP3A4

Simvastatin is a substrate of cytochrome P450 3A4. Potent inhibitors of cytochrome P450 3A4 increase the risk of myopathy and rhabdomyolysis by increasing the concentration of HMG-CoA reductase inhibitory activity in plasma during simvastatin therapy. Such inhibitors include itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone and medicinal products containing cobicistat. Concomitant administration of itraconazole resulted in a more than 10-fold increase in exposure to simvastatin acid (the active beta-hydroxyacid metabolite). Telithromycin caused an 11-fold increase in exposure to simvastatin acid.

Combination with itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone and medicinal products containing cobicistat is contraindicated, as well as gemfibrozil, ciclosporin, and danazol (see Contraindications). If treatment with potent CYP3A4 inhibitors (agents that increase AUC approximately 5-fold or greater) is unavoidable, therapy with simvastatin must be suspended (and use of an alternative statin considered) during the course of treatment. Caution should be exercised when combining simvastatin with certain other less potent CYP3A4 inhibitors: fluconazole, verapamil, or diltiazem (see Dosage and administration and Special warnings and precautions for use).

Fluconazole

Rare cases of rhabdomyolysis associated with concomitant administration of simvastatin and fluconazole have been reported (see Special warnings and precautions for use).

Ciclosporin

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ciclosporin with simvastatin; therefore, use with ciclosporin is contraindicated (see Contraindications and Special warnings and precautions for use).

Although the mechanism is not fully understood, ciclosporin has been shown to increase the AUC of HMG-CoA reductase inhibitors. The increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4 and/or OATP1B1.

Danazol

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with simvastatin; therefore, use with danazol is contraindicated. (see Contraindications and Special warnings and precautions for use).

Gemfibrozil

Gemfibrozil increases the AUC of simvastatin acid by 1.9-fold, possibly due to inhibition of the glucuronidation pathway and/or OATP1B1 (see Contraindications and Special warnings and precautions for use). Concomitant administration with gemfibrozil is contraindicated.

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 pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with systemic fusidic acid is necessary, simvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment **(see also Special warnings and precautions for use)**.

Amiodarone

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone with simvastatin (see Special warnings and precautions for use). In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone. Therefore, the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone.

Calcium channel blockers

• *Verapamil*

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of verapamil with simvastatin 40 mg or 80 mg (see Special warnings and precautions for use). In a pharmacokinetic study, concomitant administration with verapamil resulted in a 2.3-fold increase in exposure of simvastatin acid, presumably due, in part, to inhibition of CYP3A4. Therefore, the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with verapamil.

• *Diltiazem*

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of diltiazem with simvastatin 80 mg (see Special warnings and precautions for use). In a pharmacokinetic study, concomitant administration of diltiazem caused a 2.7-fold increase in exposure of simvastatin acid, presumably due to inhibition of CYP3A4. Therefore, the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with diltiazem.

• *Amlodipine*

Patients on amlodipine treated concomitantly with simvastatin have an increased risk of myopathy. In a pharmacokinetic study, concomitant administration of amlodipine caused a 1.6-fold increase in exposure of simvastatin acid. Therefore, the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amlodipine.

Lomitapide

The risk of myopathy and rhabdomyolysis may be increased by concomitant administration of lomitapide with simvastatin (see Contraindications and Special warnings and precautions for use). 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 (see Special warnings and precautions for use).

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 (see Contraindications and Special warnings and precautions for use).

Niacin (nicotinic acid)

Rare cases of myopathy/rhabdomyolysis have been associated with simvastatin co-administered with lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid). In a pharmacokinetic study, the co-administration of a single dose of nicotinic acid prolonged-release 2 g with simvastatin 20 mg resulted in a modest increase in the AUC of simvastatin and simvastatin acid and in the C_{max} of simvastatin acid plasma concentrations.

Grapefruit juice

Grapefruit juice inhibits cytochrome P450 3A4. Concomitant intake of large quantities (over 1 L daily) of grapefruit juice and simvastatin resulted in a 7-fold increase in exposure to simvastatin acid. Intake of 240 mL of grapefruit juice in the morning and simvastatin in the evening also resulted in a 1.9-fold increase. Intake of grapefruit juice during treatment with simvastatin should therefore be avoided.

Colchicine

There have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and simvastatin in patients with renal impairment. Close clinical monitoring of such patients taking this combination is advised.

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.

Effects of simvastatin on the pharmacokinetics of other medicinal products

Simvastatin does not have an inhibitory effect on cytochrome P450 3A4. Therefore, simvastatin is not expected to affect plasma concentrations of substances metabolised via cytochrome P450 3A4.

Oral anticoagulants

In two clinical studies, one in normal volunteers and the other in hypercholesterolaemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalised Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. 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.

Pregnancy and lactation

Pregnancy

Simvastatin is contraindicated during pregnancy (see Contraindications).

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. However, in an analysis of approximately 200 prospectively followed pregnancies exposed during the first trimester to simvastatin or another closely related HMG-CoA reductase inhibitor, the incidence of congenital anomalies was comparable to that seen in the general population. This number of pregnancies was statistically sufficient to exclude a 2.5-fold or greater increase in congenital anomalies over the background incidence.

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 (see Contraindications and Preclinical safety data).

Breastfeeding

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 breast-feed their infants (see Contraindications).

Fertility

No clinical trial data are available on the effects of simvastatin on human fertility. Simvastatin had no effect on the fertility of male and female rats (see Preclinical safety data).

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 postmarketing experiences.

Undesirable effects

The frequencies of the following adverse events, which have been reported during clinical studies and/or postmarketing use, are categorised based on an assessment of their incidence rates in large, long-term, placebo-controlled, clinical trials including HPS and 4S with 20,536 and 4,444 patients, respectively (see Pharmacodynamic properties). For HPS, only serious adverse events were recorded as well as myalgia, increases in serum transaminases and CK. For 4S, all the adverse events listed below were recorded. If the incidence rates on simvastatin were less than or similar to that of placebo in these trials, and there were similar reasonably causally related spontaneous report events, these adverse events are categorised as "rare".

In HPS (see Pharmacodynamic properties) involving 20,536 patients treated with 40 mg/day of simvastatin (n = 10,269) or placebo (n = 10,267), the safety profiles were comparable between patients treated with simvastatin 40 mg and patients treated with placebo over the mean 5 years of the study. Discontinuation rates due to side effects were comparable (4.8% in patients treated with simvastatin 40 mg compared with 5.1% in patients treated with placebo). The incidence of myopathy was <0.1% in patients treated with simvastatin 40 mg. Elevated transaminases (>3 x ULN confirmed by repeat test) occurred in 0.21% (n = 21) of patients treated with simvastatin 40 mg compared with 0.09% (n = 9) of patients treated with placebo.

The frequencies of adverse events are ranked according to the following: very common (>1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Rare: Anaemia

Psychiatric disorders

Very rare: Insomnia

Not known: Depression

Nervous system disorders

Rare: Headache, paraesthesia, dizziness, peripheral neuropathy

Very rare: Memory impairment

Respiratory, thoracic and mediastinal disorders

Not known: Interstitial lung disease (see Special warnings and precautions for use)

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 (see Special warnings and precautions for use), myalgia, muscle cramps

* In a clinical trial, myopathy occurred commonly in patients treated with simvastatin 80 mg/day compared to patients treated with 20 mg/day (1.0% vs 0.02%, respectively) (see Special warnings and precautions for use and Interaction with other medicinal products and other forms of interaction).

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, 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 (see Special warnings and precautions for use).

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) (see Special warnings and precautions for use "Hepatic effects"), elevated alkaline phosphatase; increase in serum CK levels (see Special warnings and precautions for use).

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

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use, including simvastatin. The reports are generally nonserious, 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 ≥5.6 mmol/L, BMI >30kg/m^2, raised triglycerides, history of hypertension).

Paediatric population

Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolaemia (n = 175), the safety and tolerability profile of the group treated with simvastatin was generally similar to that of the group treated with placebo. The long-term effects on physical, intellectual, and sexual maturation are unknown. No sufficient data are currently available after one year of treatment (see Dosage and administration, Special warnings and precautions for use, and Pharmacodynamic properties).

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Lipid modifying agents, plain, HMG CoA reductase inhibitors

ATC code: C10AA01

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 LDL-C concentrations. LDL is formed from very-low-density protein (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 HDL-C and reduces plasma TG. As a result of these changes, the ratios of total- to HDL-C and LDL- to HDL-C are reduced.

High risk of Coronary Heart Disease (CHD) or existing Coronary Heart Disease

In the Heart Protection Study (HPS), the effects of therapy with simvastatin were assessed in 20,536 patients (age 40-80 years), with or without hyperlipidaemia, and with coronary heart disease, other occlusive arterial disease or diabetes mellitus. In this study, 10,269 patients were treated with simvastatin 40 mg/day and 10,267 patients were assigned to matching placebo treatment for a mean duration of 5 years. At baseline, 6,793 patients (33%) had LDL-C levels below 116 mg/dL; 5,063 patients (25%) had levels between 116 mg/dL and 135 mg/dL; and 8,680 patients (42%) had levels greater than 135 mg/dL.

Treatment with simvastatin 40 mg/day compared with placebo significantly reduced the risk of all