

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

SIMVASTATIN TABLETS BP 20mg

Strength

SIMVASTATIN TABLETS BP 20mg

Pharmaceutical Form

Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film Coated Tablets Contains

Simvastatin BP 20mg

Excipients q.s.

Ingredients
Simvastatin
Lactose monohydrate
Maize starch
Pregelatinized starch
Sodium starch glycollate
Colloidal anhydrous silica
Butylated hydroxyl toluene
Isopropyl alcohol
Citric acid monohydrate

Ascorbic acid
Colloidal anhydrous silica
Sodium starch glycollate
Microcrystalline cellulose (Avicel PH 102)
Magnesium stearate
Hydroxy Propyl Methyl Cellulose
Purified Talc
Titanium dioxide
Ferric oxide red (CI 77491)
Ferric oxide red (CI 77492)
Polyethylene Glycol-PEG 400

3. PHARMACEUTICAL FORM

Film Coated Tablets

Description

Peach coloured, oval, biconvex, film coated tablets plain on one side & '20' embossing on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia:

SIMVASTATIN tablets are indicated, in combination with diet, to decrease elevated serum total cholesterol and LDL-cholesterol in patients with:

Primary hypercholesterolaemia,

Heterozygous familial hypercholesterolaemia, or

Mixed hyperlipidaemia when response to diet or other nonpharmacological measures alone is not adequate.

Coronary heart disease:

SIMVASTATIN tablets are indicated in patients with coronary heart disease and hypercholesterolaemia unresponsive to diet, to:

Reduce the risk of total mortality, by reducing coronary death,

Reduce the risk of non-fatal myocardial infarction,

Reduce the risk of undergoing myocardial revascularisation procedures (coronary artery bypass grafting and percutaneous transluminal coronary angioplasty), and

Slow the progression of coronary atherosclerosis.

4.2 Posology and method of administration

The dosage range is 5-80 mg/day given orally 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 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.

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 dosage, if required, should be made as specified above.

Homozygous familial hypercholesterolaemia

Based on the results of a controlled clinical study, the recommended starting dosage 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.

In patients taking lomitapide concomitantly with simvastatin, the dose of simvastatin must not exceed 40 mg/day.

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 dosage, 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 or fenofibrate, the dose of simvastatin should not exceed 10 mg/day. In patients taking amiodarone, amlodipine, verapamil, or diltiazem concomitantly with simvastatin, the dose of simvastatin should not exceed 20 mg/day.

Dosage in renal impairment

No modification of dosage should be necessary in patients with moderate renal impairment.

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

Use in the elderly

No dosage adjustment is necessary.

Use in children and adolescents (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 . Adjustments should be made at intervals of 4 weeks or more.

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

4.3 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 (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 and nefazodone and medicinal products containing cobicistat)
- Concomitant administration of gemfibrozil, ciclosporin, or danazol.
- In patients with HoFH, concomitant administration of lomitapide with doses >40 mg simvastatin

4.4 Special warnings and special 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 sections 4.8 and 5.1).

The risk of myopathy is greater in patients on simvastatin 80 mg compared with other statin-based therapies with similar LDL-C lowering efficacy. 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).

In a clinical trial in which patients at high risk of cardiovascular disease were treated with simvastatin 40 mg/day (median follow-up 3.9 years), the incidence of myopathy was approximately 0.05% for non-Chinese patients (n = 7367) compared with 0.24% for Chinese patients (n = 5468). While the only Asian population assessed in this clinical trial was Chinese, caution should be used when prescribing simvastatin to Asian patients and the lowest dose necessary should be employed.

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 section 5.2). 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 ($> 5 \times \text{ULN}$), 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 ($> 5 \times \text{ULN}$), treatment should not be started.

Whilst on treatment

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.

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 ($> 5 \times \text{ULN}$), treatment should be stopped. If muscular symptoms are severe

and cause daily discomfort, even if CK levels are $< 5 \times \text{ULN}$, treatment discontinuation may be considered. If myopathy is suspected for any other reason, treatment should be discontinued.

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.

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.

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.

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.

Consequently, regarding CYP3A4 inhibitors, the use of simvastatin concomitantly with itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone is contraindicated. 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, diltiazem . Concomitant intake of grapefruit juice and simvastatin should be avoided.

The use of simvastatin with gemfibrozil is contraindicated (see section 4.3). 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 (see sections 4.2 and 4.5). Caution

should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone.

Simvastatin must not be co-administered with fusidic acid. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. 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, amlodipine, verapamil or diltiazem should be avoided. 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 (agents that increase AUC approximately 2-5 fold), a dose adjustment of simvastatin may be necessary. For certain moderate CYP3A4 inhibitors e.g. diltiazem, a maximum dose of 20mg simvastatin is recommended.

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.

In a clinical trial (median follow-up 3.9 years) involving patients at high risk of cardiovascular disease and with well-controlled LDL-C levels on simvastatin 40 mg/day with or without ezetimibe 10 mg, there was no incremental benefit on cardiovascular outcomes with the addition of lipid-modifying doses ≥ 1 g/day) of niacin (nicotinic acid) 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.

In addition, in this trial, the incidence of myopathy was approximately 0.24% for Chinese patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg compared with 1.24% for Chinese patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg co-administered with modified-release nicotinic acid/laropiprant 2000 mg/40 mg. While the only Asian population assessed in this clinical trial was Chinese, because the incidence of myopathy is higher in Chinese than in non-Chinese patients, 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.

Hepatic effects

In clinical studies, persistent increases (to > 3 x 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 3 x ULN and are persistent, simvastatin should be discontinued. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy (see above Myopathy/Rhabdomyolysis).

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 hepatobilirubinaemia or jaundice occurs during treatment with simvastatin, promptly interrupt therapy. If an alternate aetiology is not found, do not restart treatment with simvastatin.

The product should be used with caution in patients who consume substantial quantities of alcohol. As with other lipid-lowering agents, moderate (< 3 x 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 > 30kg/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 (see section 4.8). 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.

Use in children and adolescents (10-17 years of age)

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 (see sections 4.3 and 4.6). 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.

4.5 Interaction with other FPPs and other forms of interaction

Interaction studies have only been performed in adults.

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). 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 .

Pharmacokinetic interactions

Prescribing recommendations for interacting agents are summarized in the table below (further details are provided in the text; .

Drug Interactions Associated with Risk of Myopathy/Rhabdomyolysis

Interacting agents	Prescribing recommendations
Itraconazole	Contraindicated with simvastatin
Ketoconazole	
Posaconazole	
Voriconazole	
Erythromycin	
Clarithromycin	
Telithromycin	
HIV protease inhibitors (e.g. nelfinavir)	
Boceprevir	
Telaprevir	
Nefazodone	
Cobicistat	
Ciclosporin	
Danazol	
Gemfibrozil	
Other fibrates (except fenofibrate)	Do not exceed 10 mg simvastatin daily
Fusidic acid	Is not recommended with simvastatin
Niacin (nicotinic acid) (≥ 1 g/day)	For Asian patients, not recommended with simvastatin
Amiodarone	Do not exceed 20 mg simvastatin daily
Amlodipine	
Verapamil	

Diltiazem	For patients with HoFH, do not exceed 40 mg simvastatin daily
Lomitapide	
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 and nefazodone. 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 and nefazodone is contraindicated, as well as gemfibrozil, ciclosporin, and danazol (see section 4.3). 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.

Fluconazole

Rare cases of rhabdomyolysis associated with concomitant administration of simvastatin and fluconazole have been reported.

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 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.

Danzol

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with simvastatin; therefore, use with danazol is contraindicated.

Gemfibrozil

Gemfibrozil increases the AUC of simvastatin acid by 1.9-fold, possibly due to inhibition of the glucuronidation pathway and/or OATP1B1. 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. Co-administration of this combination may cause increased plasma concentrations of both agents. 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 fusidic acid is necessary, simvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment.

Amiodarone

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone with simvastatin (see section 4.4). 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. 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. 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. 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 with 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.

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 litre 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 insufficiency. 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 Normalized 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.

4.6 Pregnancy and lactation

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. 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.

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 breast-feed their infants (see section 4.3).

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

4.7 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.

4.8 Undesirable effects

The frequencies of the following adverse events, which have been reported during clinical studies and/or post-marketing use, are categorized 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. 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 categorized as “rare”.

In HPS 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 (\geq 1/100, < 1/10), Uncommon (\geq 1/1000, < 1/100), Rare (\geq 1/10,000, < 1/1000), 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, paresthesia, dizziness, peripheral neuropathy

Very rare: memory impairment

Respiratory, thoracic and mediastinal disorders:

Not known: interstitial lung disease (see section 4.4)

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 connective 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

* 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) 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, including simvastatin.

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

Children and adolescents (10-17 years of age)

In a 48-week study involving children and adolescents (boys Tanner Stage II and above and girls who were at least one year post-menarche) 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

4.9 Overdose

To date, a few cases of overdosage 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

HMG-CoA reductase inhibitor

ATC Code

C10A A01

Pharmacodynamic effects

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed 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 treated with placebo 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 cause mortality (1328 [12.9%] for simvastatin-treated patients versus 1507 [14.7%] for patients given placebo; $p = 0.0003$), due to an 18 % reduction in coronary death rate (587 [5.7%] versus 707 [6.9%]; $p = 0.0005$; absolute risk reduction of 1.2%). The reduction in non-vascular deaths did not reach statistical significance. Simvastatin also decreased the risk of major coronary events (a composite endpoint comprised of non-fatal MI or CHD death) by 27% ($p < 0.0001$). Simvastatin reduced the need for undergoing coronary revascularization procedures (including coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) and peripheral and other non-coronary revascularization procedures by 30% ($p < 0.0001$) and 16% ($p = 0.006$), respectively. Simvastatin reduced the risk of stroke by 25% ($p < 0.0001$), attributable to a 30% reduction in ischemic stroke ($p < 0.0001$). In addition, within the subgroup of patients with diabetes, simvastatin reduced the risk of developing macrovascular complications, including peripheral revascularization procedures (surgery or angioplasty), lower limb amputations, or leg ulcers by 21% ($p = 0.0293$). The proportional reduction in event rate was similar in each subgroup of patients studied, including those without coronary disease but who had cerebrovascular or peripheral artery disease, men and women, those aged either under or over 70 years at entry into the study, presence or absence of hypertension, and notably those with LDL cholesterol below 3.0 mmol/L at inclusion.

In the Scandinavian Simvastatin Survival Study (4S), the effect of therapy with simvastatin on total mortality was assessed in 4,444 patients with CHD and baseline total cholesterol 212-309 mg/dL (5.5-8.0 mmol/L). In this multicenter, randomised, double-blind, placebo-controlled study, patients with angina or a previous myocardial infarction (MI) were treated with diet, standard care, and either simvastatin 20-40 mg/day ($n = 2,221$) or placebo ($n = 2,223$) for a median duration of 5.4

years. Simvastatin reduced the risk of death by 30% (absolute risk reduction of 3.3%). The risk of CHD death was reduced by 42% (absolute risk reduction of 3.5%). Simvastatin also decreased the risk of having major coronary events (CHD death plus hospital-verified and silent nonfatal MI) by 34%. Furthermore, simvastatin significantly reduced the risk of fatal plus nonfatal cerebrovascular events (stroke and transient ischemic attacks) by 28%. There was no statistically significant difference between groups in non-cardiovascular mortality.

The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) evaluated the effect of treatment with simvastatin 80 mg versus 20 mg (median follow-up 6.7 yrs) on major vascular events (MVEs; defined as fatal CHD, non-fatal MI, coronary revascularization procedure, non-fatal or fatal stroke, or peripheral revascularization procedure) in 12,064 patients with a history of myocardial infarction. There was no significant difference in the incidence of MVEs between the 2 groups; simvastatin 20 mg (n = 1553; 25.7%) vs. simvastatin 80 mg (n = 1477; 24.5%); RR 0.94, 95% CI: 0.88 to 1.01. The absolute difference in LDL-C between the two groups over the course of the study was 0.35 ± 0.01 mmol/L. The safety profiles were similar between the two treatment groups except that the incidence of myopathy was approximately 1.0% for patients on simvastatin 80 mg compared with 0.02% for patients on 20 mg. 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%.

Primary Hypercholesterolaemia and Combined Hyperlipidaemia

In studies comparing the efficacy and safety of simvastatin 10, 20, 40 and 80 mg daily in patients with hypercholesterolemia, the mean reductions of LDL-C were 30, 38, 41 and 47%, respectively. In studies of patients with combined (mixed) hyperlipidaemia on simvastatin 40 mg and 80 mg, the median reductions in triglycerides were 28 and 33% (placebo: 2%), respectively, and mean increases in HDL-C were 13 and 16% (placebo: 3%), respectively.

Clinical Studies in Children and Adolescents (10-17 years of age)

In a double-blind, placebo-controlled study, 175 patients (99 boys Tanner Stage II and above and 76 girls who were at least one year post-menarche) 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolaemia (heFH) were randomized to simvastatin or placebo for 24 weeks (base study). Inclusion in the study required a baseline LDL-C level between 160 and 400 mg/dL and at least one parent with an LDL-C level > 189 mg/dL. The dosage of simvastatin (once daily in the evening) was 10 mg for the first 8 weeks, 20 mg for the second 8 weeks, and 40 mg

thereafter. In a 24-week extension, 144 patients elected to continue therapy and received simvastatin 40 mg or placebo.

Simvastatin significantly decreased plasma levels of LDL-C, TG, and Apo B. Results from the extension at 48 weeks were comparable to those observed in the base study. After 24 weeks of treatment, the mean achieved LDL-C value was 124.9 mg/dL (range: 64.0-289.0 mg/dL) in the simvastatin 40 mg group compared to 207.8 mg/dL (range: 128.0-334.0 mg/dL) in the placebo group.

After 24 weeks of simvastatin treatment (with dosages increasing from 10, 20 and up to 40 mg daily at 8-week intervals), simvastatin decreased the mean LDL-C by 36.8% (placebo: 1.1% increase from baseline), Apo B by 32.4% (placebo: 0.5%), and median TG levels by 7.9% (placebo: 3.2%) and increased mean HDL-C levels by 8.3% (placebo: 3.6%). The long-term benefits of simvastatin on cardiovascular events in children with heFH are unknown.

The safety and efficacy of doses above 40 mg daily have not been studied in children with heterozygous familial hypercholesterolaemia. The long-term efficacy of simvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

5.2 Pharmacokinetic properties

Simvastatin is an inactive lactone which is readily hydrolyzed 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 metabolite 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 is taken up actively into the hepatocytes by the transporter OATP1B1.

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, which may lead to an increased risk of rhabdomyolysis

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, Maize starch, Sodium starch glycollate, Colloidal anhydrous silica, Butylated hydroxyl toluene, Citric acid monohydrate, Ascorbic acid, Colloidal anhydrous silica, Sodium starch glycollate, Microcrystalline cellulose (Avicel PH 102), Magnesium stearate, Hydroxy Propyl Methyl Cellulose, Purified Talc, Titanium dioxide, Ferric oxide, Polyethylene Glycol-PEG 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 Years

6.4 Special precautions for storage

Do not store above 30°C. Protect from light.

6.5 Nature and contents of container

Alu-PVDC blister pack of 10x10 tablets packed in carton along with Pack Insert

6.6 Instructions for use and handling and disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Milan Laboratories (India) Pvt. Ltd

Plot No. 63/67/87/35/36/64/65

J.C.I.E. LTD., Kamothe,

Panvel, Navi Mumbai,

India.

8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

04772/5679/NMR/2017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Nov 22, 2019

10. DATE OF REVISION OF THE TEXT

MILAN LABORATORIES (INDIA) PVT LTD