SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

SIMCARD 10, 10 mg, film-coated tablets

SIMCARD 20, 20 mg, film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each SIMCARD 10 film-coated tablet contains: 10 mg simvastatin.

Each SIMCARD 20 film-coated tablet contains: 20 mg simvastatin.

Contains sugar (SIMCARD 10 contains 95,2 mg lactose monohydrate per tablet. SIMCARD 20 contains 190 mg lactose monohydrate per tablet).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

Simcard 10: Pale pink coloured, oval, convex, coated tablets with "SIM 10" embossed on one side and breakline on the other side, free from cracks, mottling and chips in the tablet surface..

Simcard 20: An orange coloured, oval, convex, coated tablets with "SIM 20" embossed on one side and breakline on the other side, free from cracks, mottling and chips in the tablet surface.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia:

SIMCARD is 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:

SIMCARD is indicated in patient with coronary heart disease and hypercholesterolaemia unresponsive to diet, to:

- Reduce the risk of total morality, 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 patient must follow a cholesterol-lowering diet before initiation of, and while on SIMCARD therapy.

Hypercholesterolaemia:

Adults: Initial dose: 10 mg daily as a single dose in the evening.

The dose of SIMCARD should be reduced if LDL-cholesterol levels fall below 1,94 mmol/l, or total plasma cholesterol levels fall below 3,6 mmol/l.

Coronary heart disease:

Adults: Initial dose: 20 mg daily as a single dose in the evening.

Dosage adjustments:

If required, the dose should be adjusted at intervals of not less than 4 weeks, up to a maximum of 80 mg daily as a single dose in the evening.

SIMCARD can be taken with meals or on an empty stomach.

Dosage in renal insufficiency:

SIMCARD does not undergo significant renal excretion, therefore modification of dose should not be necessary in patient with mild to moderate renal insufficiency. In patients with severe renal insufficiency SIMCARD therapy should be closely monitored and doses above 10 mg daily should be implemented with caution.

Concomitant therapy:

SIMCARD is effective alone or in combination with bile acid sequestrants. When both medicines are prescribed, SIMCARD should be given 1 hour before or 4 hours after cholestyramine administration (see section 4.5). A maximum daily dose of 10 mg SIMCARD is recommended in patients taking cyclosporin, fibrates or niacin or concomitantly (see section 4.5).

4.3 Contraindications

Hypersensitivity to simvastatin, other HMG-CoA reductase inhibitors, or any of the excipients listed in section 6.1.

Acute or chronic liver disease.

Unexplained persistent elevations of serum transaminases.

Pregnancy and lactation (see section 4.4).

Concomitant administration of potent CYP3A4 inhibitors (medicines 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 medicines containing cobicistat) (see section 4.4 and section 4.5).

Concomitant administration of gemfibrozil, cyclosporin, or danazol (see section 4.4 and section 4.5).

In patients with HoFH, concomitant administration of lomitapide with doses > 40 mg SIMCARD (see section 4.2, section 4.4 and section 4.5).

Porphyria: Safety has not been established.

4.4 Special warnings and precautions for use

The active metabolite of SIMCARD is fetotoxic and teratogenic in rats, and it should therefore not be used in female patients of child-bearing potential.

SIMCARD is not effective in severe hypertriglyceridemia.

SIMCARD should be used with caution in patients who:

- Consume substantial amounts of alcohol and/ or who have a history of liver disease.
- May be predisposed to developing renal failure secondary to rhabdomyolysis such as in those with severe acute infection, hypertension, severe metabolic, endocrine or electrolyte disorders, uncontrolled seizures, major surgery or trauma. There is an increased risk of developing renal failure if rhabdomyolysis occurs.
- Have severe renal impairment.

Hepatic effects:

Liver function tests, including serum transaminase determinations are recommended prior to initiation of SIMCARD therapy and periodically until one year after the last elevation in dose. SIMCARD should be discontinued if the rise in transaminase levels is persistent and/ or increases to three times or more the upper limit of normal (ULN).

Myopathy:

SIMCARD, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and very rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma (i.e., elevated SIMCARD and simvastatin acid plasma levels), which may be due, in part, to interacting medicines that interfere with SIMCARD metabolism and/or transporter pathways (see section 4.5).

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related. Clinical trials indicates that the incidence of myopathy is 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 medicines were excluded.

A clinical trial including patients with a history of myocardial infarction and treated with simvastatin 80 mg/day (mean follow-up 6,7 years), showed an incidence of myopathy of approximately 1,0 % compared with 0,02 % for patients on simvastatin 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 section 4.8 and section 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 SIMCARD should only be used in patients with severe hypercholesterolaemia and at high risk for cardiovascular complications who have not achieved their treatment goals on lower doses. In patients taking doses of 80 mg SIMCARD for whom an interacting medicine is needed, a lower dose of SIMCARD or an alternative statin-based regimen with less potential for medicine-medicine interactions should be used (see below Measures to reduce the risk of myopathy caused by medicine interactions and section 4.2, section 4.3 and section 4.5).

Reducing the risk of myopathy:

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. cyclosporin) 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) SIMCARD 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 doses of SIMCARD 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.

General measures:

Before the treatment

Patients starting therapy with SIMCARD should be advised of the risk of myopathy and should report promptly, unexplained muscle pain, tenderness or weakness. A creatinine kinase (CK) level above ten times the Upper Limit of Normal (ULN) in a patient, with unexplained symptoms, indicates myopathy. SIMCARD should be discontinued if myopathy is diagnosed or suspected.

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 (> 5x ULN), treatment should not be started.

Whilst on treatment

If muscle pain, weakness or cramps occur whilst a patient is receiving treatment with a statin, their CK levels should be measured. If these levels are found, in the absence of strenuous exercise, to be significantly elevated (> 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 section 4.8).

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 section 5.1). 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 SIMCARD 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 medicine interactions:

The benefits and risks of using SIMCARD concomitantly with immunosuppressants, fibrates (except fenofibrate) or lipid-lowering doses of niacin should be carefully considered, and the dose of SIMCARD should generally not exceed 10 mg daily.

Caution should be used when prescribing fenofibrate with SIMCARD, as either medicine can cause myopathy when given alone.

The risk of myopathy and rhabdomyolysis is significantly increased by concomitant use of SIMCARD with potent inhibitors of CYP3A4 (such as itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, nefazodone, medicines containing cobicistat), as well as gemfibrozil, cyclosporin, and danazol. Use of these medicines is contraindicated (see section 4.3).

In patients receiving cyclosporin, SIMCARD should be temporarily discontinued if systemic azole derivative antifungal therapy is required.

The risk of myopathy and rhabdomyolysis is also increased by concomitant use of amiodarone, amlodipine, verapamil, or diltiazem with certain doses of SIMCARD (see section 4.2 and section 4.5). The risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of fusidic acid with statins (see section 4.5). For patients with HoFH, this risk may be increased by concomitant use of lomitapide with SIMCARD.

Consequently, regarding CYP3A4 inhibitors, the use of SIMCARD concomitantly with itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone, and medicines containing cobicistat is contraindicated (see section 4.3 and section 4.5). If treatment with potent CYP3A4 inhibitors (medicines that increase AUC approximately 5-fold or greater) is unavoidable, therapy with SIMCARD must be suspended (and use of an alternative statin considered) during the course of treatment. Moreover, caution should be exercised when combining SIMCARD with certain other less potent

CYP3A4 inhibitors: fluconazole, verapamil, diltiazem (see section 4.2 and section 4.5). Concomitant intake of grapefruit juice and SIMCARD should be avoided.

The use of SIMCARD with gemfibrozil is contraindicated (see section 4.3).

SIMCARD must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination (see section 4.5). 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 SIMCARD and fusidic acid should only be considered on a case by case basis and under close medical supervision.

The combined use of SIMCARD at doses higher than 20 mg daily with amiodarone, amlodipine, verapamil, or diltiazem should be avoided. In patients with HoFH, the combined use of SIMCARD at doses higher than 40 mg daily with lomitapide must be avoided (see section 4.2, section 4.3 and section 4.5).

Patients taking other medicines labelled as having a moderate inhibitory effect on CYP3A4 concomitantly with SIMCARD, particularly higher SIMCARD doses, may have an increased risk of myopathy. When co-administering SIMCARD with a moderate inhibitor of CYP3A4 (medicines that increase AUC approximately 2- to 5-fold), a dose adjustment of SIMCARD may be necessary. For certain moderate CYP3A4 inhibitors e.g. diltiazem, a maximum dose of 20 mg SIMCARD is recommended (see section 4.2).

Simvastatin as in SIMCARD is a substrate of the Breast Cancer Resistant Protein (BCRP) efflux transporter. Concomitant administration of medicines that are inhibitors of BCRP (e.g. elbasvir and grazoprevir) may lead to increased plasma concentrations of SIMCARD and an increased risk of myopathy; therefore, a dose adjustment of SIMCARD should be considered depending on the prescribed dose. Co-administration of elbasvir and grazoprevir with SIMCARD has not been studied; however, the dose of SIMCARD should not exceed 20 mg daily in patients receiving concomitant treatment with medicines containing elbasvir or grazoprevir (see section 4.5).

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.

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, indicates that there was no incremental benefit on cardiovascular outcomes with the addition of lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid). Therefore, medical practitioners contemplating combined therapy with SIMCARD and lipid-modifying doses (≥ 1 g/day) of niacin (nicotinic acid) or medicines 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 medicines 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 SIMCARD 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 maybe similar to niacin.

Daptomycin

Cases of myopathy and/or rhabdomyolysis have been reported with HMG-CoA reductase inhibitors (e.g. simvastatin as in SIMCARD) co-administered with daptomycin. Caution should be used when prescribing HMG-CoA reductase inhibitors with daptomycin, as either medicine can cause myopathy and/or rhabdomyolysis when given alone. Consideration should be given to temporarily suspend SIMCARD in patients taking daptomycin unless the benefits of concomitant administration outweigh the risk. Consult the professional information of daptomycin to obtain further information about this potential interaction with HMG-CoA reductase inhibitors (e.g. simvastatin as in SIMCARD) and for further guidance related to monitoring (see section 4.5).

Hepatic effects

Clinical studies indicated persistent increases (to > 3 x ULN) in serum transaminases in a few adult patients who received simvastatin as in SIMCARD. However, when treatment is interrupted or discontinued in these patients, the transaminase levels 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, SIMCARD should be discontinued. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy (see above Myopathy/Rhabdomyolysis).

Fatal and non-fatal hepatic failure in patients taking statins, including SIMCARD may occur. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with SIMCARD, promptly interrupt therapy. If an alternate aetiology is not found, do not restart SIMCARD.

SIMCARD should be used with caution in patients who consume substantial quantities of alcohol.

As with other lipid-lowering medicines, moderate (< 3 x ULN) elevations of serum transaminases have been reported following therapy with simvastatin as in SIMCARD. These changes appeared soon after initiation of therapy, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

Diabetes mellitus

Some evidence suggests that statins as a class raise blood glucose and, in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5,6 to 6,9 mmol/L, BMI > 30 kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Interstitial lung disease

Cases of interstitial lung disease have been reported with some statins, including simvastatin as in SIMCARD, 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.

Paediatric population

Safety and effectiveness of simvastatin as in SIMCARD 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 as in SIMCARD 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 SIMCARD therapy (see section 4.3 and section 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. SIMCARD has not been studied in patients younger than 10 years of age, nor in pre-pubertal children and pre-menarchal girls.

Excipients

SIMCARD contains lactose monohydrate. Patients with rare hereditary problems of fructose intolerance, galactose intolerance, galactosaemia or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Multiple mechanisms may contribute to potential interactions with HMG-CoA reductase inhibitors. Medicines including herbal medicines that inhibit certain enzymes (e.g. CYP3A4) and/or transporter (e.g. OATP1B) pathways may increase SIMCARD and simvastatin acid plasma concentrations and may lead to an increased risk of myopathy/rhabdomyolysis.

Consult the professional information of all concomitantly used medicines to obtain further information about their potential interactions with SIMCARD and/or the potential for enzyme or transporter alterations and possible adjustments to dose and regimens.

Pharmacodynamic interaction

Interactions with lipid-lowering medicines 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 SIMCARD plasma levels (see below Pharmacokinetic interactions and section 4.3 and section 4.4). When SIMCARD and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each medicine. Adequate pharmacovigilance and pharmacokinetic data are not available for other fibrates. Rare cases of myopathy/rhabdomyolysis have been associated with SIMCARD co-administered with lipid-modifying doses (≥ 1 g/day) of niacin (see section 4.4).

Pharmacokinetic interactions

Prescribing recommendations for interacting medicines are summarised in the table below (further details are provided in the text; see also section 4.3 and section 4.4).

Medicine Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Medicine Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis	
Interacting medicines	Prescribing recommendations
Potent CYP3A4 inhibitors, e.g. Itraconazole Ketoconazole Posaconazole Voriconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors (e.g. nelfinavir) Boceprevir Telaprevir Nefazodone Cobicistat Cyclosporin Danazol Gemfibrozil	Contraindicated with SIMCARD
Other fibrates (except fenofibrate)	Do not exceed 10 mg SIMCARD daily
Fusidic acid	Is not recommended with SIMCARD
Niacin (nicotinic acid) (≥ 1 g/day)	For Asian patients, not recommended with SIMCARD
Amiodarone Amlodipine Verapamil Diltiazem Elbasvir Grazoprevir	Do not exceed 20 mg SIMCARD daily

Medicine Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis	
Interacting medicines	Prescribing recommendations
Lomitapide	For patients with HoFH, do not exceed 40 mg SIMCARD daily
Daptomycin	It should be considered to temporarily suspend SIMCARD in patients taking daptomycin unless the benefits of concomitant administration outweigh the risk (see section 4.4)
Ticagrelor	Doses greater than 40 mg SIMCARD daily are not recommended
Grapefruit juice	Avoid grapefruit juice when taking SIMCARD

Effects of other medicines on SIMCARD

Interactions involving inhibitors of CYP3A4

SIMCARD 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 SIMCARD therapy. Such inhibitors include itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, nefazodone and medicines containing cobicistat. Concomitant administration of itraconazole resulted in a more than 10-fold increase in exposure to simvastatin acid (the active beta-hydroxy acid 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 medicines containing cobicistat is contraindicated, as well as gemfibrozil, cyclosporin, and danazol (see section 4.3). If treatment with potent CYP3A4 inhibitors (medicines that increase AUC approximately 5-fold or greater) is unavoidable, therapy with SIMCARD must be suspended (and use of an alternative statin considered) during the course of treatment. Caution should be exercised when combining SIMCARD with certain other less potent CYP3A4 inhibitors: fluconazole, verapamil, or diltiazem (see section 4.2 and section 4.4).

Fluconazole

Rare cases of rhabdomyolysis associated with concomitant administration of SIMCARD and fluconazole have been reported (see section 4.4).

Cyclosporin

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporin with SIMCARD; therefore, use with cyclosporin is contraindicated (see section 4.3 and section 4.4). Although the mechanism is not fully understood, cyclosporin 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 SIMCARD; therefore, use with danazol is contraindicated (see section 4.3 and section 4.4).

Gemfibrozil

Gemfibrozil increases the AUC of simvastatin acid by 1,9-fold, possibly due to inhibition of the glucuronidation pathway and/or OATP1B1 (see section 4.3 and section 4.4). 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 pharmacodynamics or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. Co-administration of this combination may cause increased plasma concentrations of both medicines.

If treatment with systemic fusidic acid is necessary, SIMCARD treatment should be discontinued throughout the duration of the fusidic acid treatment. Also see section 4.4.

Amiodarone

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone with SIMCARD (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 SIMCARD 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 doses of 40 mg or 80 mg SIMCARD (see section 4.4). 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 SIMCARD 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 doses of 80 mg SIMCARD (see section 4.4). 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 SIMCARD should not exceed 20 mg daily in patients receiving concomitant treatment with diltiazem.

Amlodipine

Patients on amlodipine treated concomitantly with SIMCARD 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 SIMCARD should not exceed 20 mg daily in patients receiving concomitant treatment with amlodipine.

Lomitapide

The risk of myopathy and rhabdomyolysis may be increased by concomitant administration of lomitapide with SIMCARD (see section 4.3 and section 4.4). Therefore, in patients with HoFH, the dose of SIMCARD must not exceed 40 mg daily in patients receiving concomitant treatment with lomitapide.

Moderate Inhibitors of CYP3A4:

Patients taking other medicines labelled as having a moderate inhibitory effect on CYP3A4 concomitantly with SIMCARD, particularly higher SIMCARD doses, may have an increased risk of myopathy (see section 4.4).

Inhibitors of the Transport Protein OATP1B1:

Simvastatin acid is a substrate of the transport protein OATP1B1. Concomitant administration of medicines that are inhibitors of the transport protein OATP1B1 may lead to increased plasma concentrations of simvastatin acid and an increased risk of myopathy (see section 4.3 and section 4.4).

Inhibitors of Breast Cancer Resistant Protein (BCRP):

Concomitant administration of medicines that are inhibitors of BCRP, including products containing elbasvir or grazoprevir, may lead to increased plasma concentrations of SIMCARD and an increased risk of myopathy (see section 4.4).

Niacin (nicotinic acid):

Rare cases of myopathy/rhabdomyolysis have been associated with SIMCARD 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 may resulted in a modest increase in the AUC of SIMCARD and simvastatin acid and in the C_{max} of simvastatin acid plasma concentrations. Therefore, a maximum dose of 10 mg SIMCARD daily is recommended in patients taking lipid lowering doses of niacin (nicotinic acid).

Ticagrelor:

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

Grapefruit juice:

Intake of grapefruit juice during treatment with SIMCARD should be avoided.

Colchicine:

Myopathy and rhabdomyolysis with the concomitant administration of colchicine and SIMCARD in patients with renal impairment might occur. Close clinical monitoring of such patients taking this combination is advised.

Daptomycin:

The risk of myopathy and/or rhabdomyolysis may be increased by concomitant administration of HMG-CoA reductase inhibitors (e.g. SIMCARD) and daptomycin (see section 4.4).

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 SIMCARD.

Effects of SIMCARD on the pharmacokinetics of other medicines:

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

Oral anticoagulants:

A possible increase in the anticoagulant effect of the coumarin anticoagulants (e.g. warfarin) may occur. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting SIMCARD 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 SIMCARD is changed or discontinued, the same procedure should be repeated. SIMCARD therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Digoxin:

SIMCARD may cause increase in digoxin levels.

Bile acid sequestrants:

SIMCARD should be taken 1 hour before or 4 hours after cholestyramine.

Concurrent use may decrease the bioavailability of SIMCARD.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

The active metabolite of SIMCARD is fetotoxic and teratogenic in rats, and it should therefore not be used in female patients of child-bearing potential.

Pregnancy

SIMCARD is contraindicated during pregnancy (see section 4.3).

Safety in pregnant women has not been established. No controlled clinical trials with SIMCARD have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received.

Maternal treatment with SIMCARD 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 medicines during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia. For these reasons, SIMCARD must not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with SIMCARD must be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see sections 4.3).

Breastfeeding

It is not known whether SIMCARD or its metabolites are excreted in human milk. Because many medicines are excreted in human milk and because of the potential for serious adverse reactions, women taking SIMCARD must not breastfeed their infants (see section 4.3).

Fertility

No clinical trial data are available on the effects of SIMCARD on human fertility. Simvastatin as in SIMCARD had no effect on the fertility of male and female rats.

4.7 Effects on ability to drive and use machines

SIMCARD 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 may occur.

4.8 Undesirable effects

Blood and lymphatic disorders:

Less frequent: anaemia

Frequency unknown: neutropenia

Immune system disorders:

Less Frequent: anaphylaxis

Metabolism and nutrition disorders:

Frequency unknown: mass gain has been reported

Psychiatric disorders:

Less frequent: insomnia

Frequency unknown: depression

Nervous system disorders:

Less frequent: headache, dizziness, fatigue, paraesthesia, peripheral neuropathy, memory impairment

Eye disorders:

Less frequent: vision blurred, visual impairment

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: interstitial lung disease (see section 4.4)

Gastro intestinal disorders:

Less frequent: constipation, diarrhoea, nausea, vomiting, flatulence, dyspepsia, abdominal pain, cramps, pancreatitis

Hepato-biliary disorders:

Less frequent: hepatitis/jaundice, fatal and non-fatal hepatic failure

Skin and subcutaneous tissue disorders:

Less frequent: skin rash, alopecia, pruritis, lichenoid drug eruptions

Musculoskeletal and connective tissue disorders:

Frequent: myalgia, muscle cramps

Less Frequent: myopathy, myositis, rhabdomyolysis presenting as muscle pain with elevated creatine phosphokinase and myoglobinuria leading to renal failure, muscle rupture

Frequency unknown: 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 medicines (see section 4.4).

Reproductive system and breast disorders:

Less frequent: gynecomastia

Frequency unknown: erectile dysfunction

General disorders and administration site conditions:

Less frequent: asthenia

An apparent hypersensitivity syndrome, reactions may include angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, increased erythrocyte sedimentation rate, eosinophilia, arthritis, arthralgia, urticaria, photosensitivity, fever, flushing, malaise, and dyspnoea.

Investigations:

Less frequent: increases in serum transaminases (alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transpeptidase) (see section 4.4), elevated alkaline phosphatase; increase in serum CK levels (see section 4.4).

Laboratory test findings:

Liver function test abnormalities have generally been mild and transient. Increases in serum creatinine kinase (CK) levels, derived from skeletal muscle, have been reported (see section 4.4).

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

Cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use, including simvastatin as in SIMCARD, has been reported. 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 > 30 kg/m^2, raised triglycerides, history of hypertension).

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

(See section 4.4 and section 4.8)

General measures should be adopted and liver should be monitored.

Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 7.5 Serum-cholesterol reducers

ATC-Code: C10A A01

Simvastatin is a cholesterol-lowering agent derived synthetically from a fermentation product of *Aspergillus terreus.* After oral ingestion simvastatin, an inactive lactone, is hydrolysed to the corresponding beta-hydroxyacid, the active form. This is a principal metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme that catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol. As a result, simvastatin, reduces total plasma cholesterol, low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL)-cholesterol concentrations. Apolipoprotein B is also decreased. In addition, simvastatin moderately increases high-density lipoprotein (HDL)-cholesterol and variably reduces plasma triglycerides.

Pharmacokinetics:

There is extensive first-pass extraction by the liver, with oral bioavailability of the active medicine or metabolites being less than 5 %. More than 95 % of simvastatin and its beta-hydroxy metabolite are bound to plasma proteins. Following an oral dose, peak plasma concentrations of simvastatin are seen in 1 to 2 hours. Simvastatin is excreted primarily via the liver, and less than 13 % of its metabolites are excreted in the urine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

ascorbic acid, butylhydroxyanisole, citric acid monohydrate, lactose monohydrate, magnesium stearate, microcrystalline cellulose pH 101, pregelatinized starch

Tablet coating:

Opadry Pink 06A540007 and Opadry Beige 06A570000 consists of: ferric oxide, red (E172), ferric oxide, yellow (E172), hypromellose 5 cps (E464), hypromellose 15 cps (E464), talc (E553b), titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Polyethylene (HDPE) containers and closures:

Keep container tightly closed. Store in a dry place, below 25 ˚C. Protect from light.

Do not remove the blisters from the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

White opaque polyethylene (HPDE) containers and closures (tamper evident) containing 28/30 tablets or white opaque PVC/ aluminium blister packs containing 28/30 tablets per carton.

6.6 Special precautions for disposal

None.

7 HOLDER OF CERTIFICATE OF REGISTRATION

iPharma (Pty) Ltd.

124 Elevation Avenue, Randjesfontein

MIDRAND, 1683, SOUTH AFRICA

8 REGISTRATION NUMBER(S)

SIMCARD 10: 36/7.5/0215

SIMCARD 20: 36/7.5/0216

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: July 2005

10 DATE OF REVISION OF THE TEXT

26 July 2021