PROFESSIONAL INFORMATION

SIMVACOR RANGE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

SIMVACOR 10 mg film coated tablets

SIMVACOR 20 mg film coated tablets

SIMVACOR 40 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each SIMVACOR 10 mg film coated tablet contains 10 mg simvastatin.

Each SIMVACOR 20 mg film coated tablet contains 20 mg simvastatin.

Each SIMVACOR 40 mg film coated tablet contains 40 mg simvastatin.

SIMVACOR contains sugar (each 10 mg tablet contains 67,92 mg lactose monohydrate, each 20 mg tablet contains 135,84 mg lactose monohydrate and each 40 mg tablet contains 271,68 mg lactose monohydrate).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablets.

SIMVACOR 10 mg: White, round (6 mm in diameter), slightly biconvex, bevel-edged, film coated tablet.

SIMVACOR 20 mg: White, round (8 mm in diameter), slightly biconvex, bevel-edged, film coated tablet.

SIMVACOR 40 mg: White, round (11 mm in diameter), slightly biconvex, bevel-edged, one side scored, film coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia:

SIMVACOR 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 non-pharmacological measures alone is not adequate.

Coronary Heart Disease:

SIMVACOR is 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)
- 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, SIMVACOR therapy.

Hypercholesterolaemia:

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

The dose of SIMVACOR 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/day 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.

Special populations

Dosage in renal insufficiency:

SIMVACOR does not undergo significant renal excretion; therefore, modification of dose should not be necessary in patients with mild to moderate renal insufficiency. In patients with severe renal insufficiency (creatinine clearance less than 30 ml/min) SIMVACOR therapy should be closely monitored and doses above 10 mg/day should be implemented with caution.

Concomitant therapy:

SIMVACOR is effective alone or in combination with bile acid sequestrants.

When both medicines are prescribed, SIMVACOR should be given 1 hour before or 4 hours after cholestyramine administration (see section 4.5).

A maximum daily dose of 10 mg SIMVACOR is recommended in patients taking ciclosporin, fibrates or niacin concomitantly (see section 4.5).

Method of administration

Oral use.

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

Missed dose:

Doctors should advise patients who forget to take SIMVACOR to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the

missed dose.

4.3 Contraindications

- Hypersensitivity to simvastatin, other HMG-CoA reductase inhibitors, or to any of the ingredients of SIMVACOR.
- Acute or chronic liver disease.
- Unexplained persistent elevations of serum transaminases.
- Porphyria.
- Pregnancy and lactation (see sections 4.4 and 4.6).
- 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 SIMVACOR (see section 4.2, section 4.4 and section 4.5).

4.4 Special warnings and precautions for use

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

Use in paediatric patients is not recommended, as safety and efficacy have not been established.

SIMVACOR is not effective in severe hypertriglyceridaemia.

There have been rare reports of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with the use of statins, such as SIMVACOR. These symptoms are generally not serious and are reversible upon discontinuation.

SIMVACOR 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, hypotension, 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 SIMVACOR therapy and periodically until one year after the last elevation in dose.
Patients titrated to an 80 mg dose should receive an additional test at 3 months.
SIMVACOR 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:

SIMVACOR, 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 SIMVACOR and simvastatin acid plasma levels), which may be due, in part, to interacting medicines that interfere with SIMVACOR 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 SIMVACOR 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 SIMVACOR for whom an interacting medicine is needed, a lower dose of SIMVACOR 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) SIMVACOR 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 SIMVACOR 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.

1. *General measures:*

Before the treatment

Patients starting therapy with SIMVACOR should be advised of the risk of myopathy and should report, promptly, unexplained muscle pain, tenderness or weakness. A creatinine kinase (CK) level above 10 times the Upper Limit of Normal (ULN) in a patient, with unexplained symptoms, indicates myopathy. SIMVACOR 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 SIMVACOR should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

2. *Measures to reduce the risk of myopathy caused by medicine interactions*

The benefits and risks of using SIMVACOR concomitantly with immunosuppressant's, fibrates (except fenofibrate) or lipid-lowering doses of niacin should be carefully considered, and the dose of SIMVACOR should generally not exceed 10 mg/day.

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

The risk of myopathy and rhabdomyolysis is significantly increased by concomitant use of SIMVACOR 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 ciclosporin, SIMVACOR should be temporarily discontinued if systemic azole derivative-antifungal therapy is required.

Concomitant administration with certain doses of SIMVACOR with amiodarone, amlodipine, calcium channel blockers (e.g. verapamil and diltiazem) increases the risk of myopathy and rhabdomyolysis (see section 4.2 and section 4.5) and is therefore not recommended. 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 SIMVACOR.

Consequently, regarding CYP3A4 inhibitors, the use of SIMVACOR 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 SIMVACOR must be suspended (and use of an alternative statin considered) during the course of treatment. Moreover, caution should be exercised when combining SIMVACOR with certain other less potent CYP3A4 inhibitors: fluconazole, verapamil, diltiazem (see section 4.2 and section 4.5). Concomitant intake of grapefruit juice and SIMVACOR should be avoided.

Concomitant use with gemfibrozil is contraindicated (see section 4.3).

SIMVACOR 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 SIMVACOR and fusidic acid should only be considered on a case by case basis and under close medical supervision.

The combined use of SIMVACOR at doses higher than 20 mg daily with amiodarone, amlodipine, verapamil, or diltiazem should be avoided. In patients with HoFH, the combined use of SIMVACOR 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 SIMVACOR, particularly higher SIMVACOR doses, may have an increased risk of myopathy. When co-administering SIMVACOR with a moderate inhibitor of CYP3A4 (medicines that

increase AUC approximately 2- to 5-fold), a dose adjustment of SIMVACOR may be necessary. For certain moderate CYP3A4 inhibitors e.g. diltiazem, a maximum dose of 20 mg SIMVACOR is recommended (see section 4.2).

Simvastatin (as in SIMVACOR) 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 simvastatin and an increased risk of myopathy; therefore, a dose adjustment of SIMVACOR should be considered depending on the prescribed dose. Co-administration of elbasvir and grazoprevir with SIMVACOR has not been studied; however, the dose of SIMVACOR 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 SIMVACOR 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 SIMVACOR 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.

Daptomycin

Cases of myopathy and/or rhabdomyolysis have been reported with HMG-CoA reductase inhibitors (e.g. simvastatin as in SIMVACOR) 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 SIMVACOR 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 SIMVACOR) 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 SIMVACOR). 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, SIMVACOR 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 SIMVACOR may occur. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with SIMVACOR, promptly interrupt therapy. If an alternate aetiology is not found, do not restart SIMVACOR.

SIMVACOR 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 SIMVACOR. 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 SIMVACOR, 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.

Skeletal muscle effects:

Risk of myasthenia gravis and ocular myasthenia.

Information on excipients of SIMVACOR:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Paediatric population

Safety and effectiveness of simvastatin (as in SIMVACOR) 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 SIMVACOR 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. SIMVACOR 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 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 SIMVACOR 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 SIMVACOR 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 simvastatin (as in SIMVACOR) plasma levels (see below Pharmacokinetic interactions and section 4.3 and section 4.4). When SIMVACOR 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 SIMVACOR 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	
Interacting medicines	Prescribing recommendations
Potent CYP3A4 inhibitors, e.g. Itraconazole Ketoconazole	Contraindicated with SIMVACOR

Posaconazole Voriconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors (e.g. nelfinavir) Boceprevir Telaprevir Nefazodone Cobicistat Cyclosporin Danazol Gemfibrozil	
Other fibrates (except fenofibrate)	Do not exceed 10 mg SIMVACOR daily
Fusidic acid	Not recommended with SIMVACOR
Niacin (nicotinic acid) (≥ 1 g/day)	For Asian patients, not recommended with SIMVACOR
Amiodarone Amlodipine Verapamil Diltiazem Elbasvir Grazoprevir	Do not exceed 20 mg SIMVACOR daily
Lomitapide	For patients with HoFH, do not exceed 40 mg SIMVACOR daily
Daptomycin	It should be considered to temporarily suspend SIMVACOR in patients taking

	daptomycin unless the benefits of concomitant administration outweigh the risk (see section 4.4)
Ticagrelor	SIMVACOR doses greater than 40 mg daily are not recommended
Grapefruit juice	Avoid grapefruit juice when taking SIMVACOR

Effects of other medicines on SIMVACOR

Interactions involving inhibitors of CYP3A4

Concomitant administration of medicines that inhibit cytochrome P450 isoenzyme CYP3A4 may result in high plasma levels of SIMVACOR, thus increasing the risk of myopathy and rhabdomyolysis by increasing the concentration of HMG-CoA reductase inhibitory activity in plasma during SIMVACOR therapy.

Medicines that inhibit cytochrome P450 isoenzyme CYP3A4 include: amiodarone, calcium channel blockers (e.g. verapamil and diltiazem), ciclosporin, itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV-protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, medicines containing cobicistat and nefazodone.

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 SIMVACOR must be suspended (and use of an alternative statin considered) during the course of treatment. Caution should be exercised when

combining SIMVACOR 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 therapy of SIMVACOR and fluconazole have been reported (see section 4.4).

Cyclosporin:

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporin with SIMVACOR; 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 SIMVACOR; 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 pharmacodynamic 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, SIMVACOR treatment should be discontinued throughout the duration of the fusidic acid treatment (see section 4.4).

Amiodarone:

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone with SIMVACOR (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 SIMVACOR 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 SIMVACOR (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 SIMVACOR 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 SIMVACOR (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 SIMVACOR should not exceed 20 mg daily in patients receiving concomitant treatment with diltiazem.

Amlodipine:

Patients on amlodipine treated concomitantly with SIMVACOR 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 SIMVACOR 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 SIMVACOR (see section 4.3 and section 4.4). Therefore, in patients with HoFH, the dose of SIMVACOR 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 SIMVACOR, particularly higher SIMVACOR 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 SIMVACOR and an increased risk of myopathy (see section 4.4).

Niacin (nicotinic acid):

Rare cases of myopathy/rhabdomyolysis have been associated with SIMVACOR 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 simvastatin and simvastatin acid and in the C_{max} of simvastatin acid plasma concentrations. A maximum dose of 10 mg SIMVACOR daily is recommended in patients taking lipid lowering doses of niacin (nicotinic acid).

Ticagrelor:

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

Grapefruit juice:

Grapefruit juice inhibits the cytochrome P450 isoenzyme CYP3A4 which may result in high plasma levels of SIMVACOR and possibly lead to rhabdomyolysis (see section 4.2). Intake of grapefruit juice during treatment with SIMVACOR should be avoided.

Colchicine:

Myopathy and rhabdomyolysis with the concomitant administration of colchicine and SIMVACOR 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. SIMVACOR) 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 SIMVACOR.

Effects of SIMVACOR on the pharmacokinetics of other medicines:

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

Coumarin-derivatives (e.g. Warfarin):

A possible increase in the anticoagulant effect of the coumarin anticoagulants may occur. Patients taking a coumarin anticoagulant should have their INR (international normalised ratio) determined before starting SIMVACOR therapy. The INR should be monitored frequently enough in the early stages of therapy until stabilised. Once a stable INR has been documented, INR can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. When there is a dose adjustment of SIMVACOR, this procedure should be repeated.

Digoxin:

SIMVACOR may cause increases in digoxin levels.

Bile acid sequestrants:

SIMVACOR should be taken 1 hour before or 4 hours after cholestyramine. Concurrent use may decrease the bioavailability of SIMVACOR.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

The active metabolite of SIMVACOR is fetotoxic and teratogenic in rats, and it should therefore not be used in female patients of childbearing potential.

Pregnancy

SIMVACOR is contraindicated in pregnancy (see section 4.3). Safety in pregnancy has not been established.

No controlled clinical trials with SIMVACOR 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 SIMVACOR 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, SIMVACOR must not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with SIMVACOR 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

SIMVACOR is contraindicated in lactation (see section 4.3). Safety during lactation has not been established.

It is not known whether SIMVACOR 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 SIMVACOR must not breastfeed their infants (see section 4.3).

Fertility

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

4.7 Effects on ability to drive and use machines

SIMVACOR has no or negligible influence on the ability to drive and use machines.

Dizziness or headaches may occur, therefore when driving vehicles or operating machinery this should be taken into account.

4.8 Undesirable effects

a). *Tabulated summary of adverse reactions*

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Less frequent Frequency unknown	Anaemia Neutropenia
Immune system disorders	Frequency unknown	Hypersensitivity reactions that include angioedema, anaphylaxis, lupus-like syndrome, polymyalgia rheumatica, vasculitis, thrombocytopenia, increased erythrocyte sedimentation rate, eosinophilia, arthritis, arthralgia, urticaria, photosensitivity, fever, flushing, malaise and dyspnoea
Metabolism and nutrition disorders	Less frequent	Increase serum glucose levels
Psychiatric disorders	Less frequent Frequency unknown	Insomnia, memory impairment and confusion Depression
Nervous system disorders	Less frequent Frequency unknown	Headache, dizziness, fatigue, asthenia, dysgeusia, paraesthesia, peripheral neuropathy Myasthenia gravis
Eye disorders	Less frequent Frequency unknown	Blurred vision, vision impairment Ocular myasthenia
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Interstitial lung disease

Gastrointestinal disorders	Less frequent	Constipation, diarrhoea, nausea, flatulence, abdominal pain and cramps, vomiting, dyspepsia and pancreatitis
Hepatobiliary disorders	Less frequent	Hepatitis, jaundice, fatal and non-fatal hepatic failure
Skin and subcutaneous tissue disorders	Less frequent	Skin rash, alopecia, pruritus, lichenoid drug eruptions
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent Frequency unknown	Myalgia, muscle cramps Myopathy, myositis, rhabdomyolysis presenting as muscle pain with elevated creatine phosphoskinase and myoglobinuria leading to renal failure Tendinopathy, sometimes complicated by rupture; immune-mediated necrotizing myopathy (IMNM)*
Reproductive system and breast disorders	Less frequent Frequency unknown	Gynecomastia Erectile dysfunction
General disorders and administrative site conditions	Less frequent Frequency unknown	Asthenia Mass gain

Investigations	Less frequent	Marked and persistent increases of serum transaminases and elevated alkaline phosphatase and gamma-glutamyl transpeptidase have been reported. Liver function test abnormalities have generally been mild and transient. Increases in serum creatine 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.
	Frequency unknown	Cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use, including simvastatin as in SIMVACOR, has been reported. 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).

* 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 (see section 4.4).

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).

c). *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 professionals are asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by following the link: https://www.sahpra.org.za/Publications/Index/8. An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

See sections 4.4 and 4.8.

Management of overdose:

General measures should be adopted and liver function should be monitored.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA-reductase inhibitor

ATC code: C10AA01

Pharmacological classification: A.7.5 Serum cholesterol reducers.

Mechanism of action

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 principle 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.

5.2 Pharmacokinetic properties

Absorption:

There is extensive first-pass extraction by the liver, with oral bioavailability of the active medicine or metabolites being less than 5 %. Following an oral dose, peak plasma concentrations of simvastatin are seen in 1 to 2 hours.

Distribution:

More than 95 % of simvastatin and its beta-hydroxy metabolite are bound to plasma proteins.

Elimination:

Simvastatin has a half-life of about 12 hours. Simvastatin is excreted primarily via the liver, and less than 13 % of its metabolites are excreted in the urine.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores:

Ascorbic acid

ButylhydroxyanisoleCitric acid anhydrous

Lactose monohydrate

Magnesium stearate

Maize starch

Microcrystalline cellulose

Starch pre-gelatinised

Film coating:

Hypromellose

Propylene Glycol

Talc

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 ºC, in a dry place. Protect from light.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

Blister packs consisting of thermo formed PVC/PE/PVDC film and heat sealing aluminium foil.

6.6 Special precautions for disposal

No special precautions.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBER(S)

SIMVACOR 10 mg: RSA S4 A35/7.5/0237

SIMVACOR 20 mg: RSA S4 A35/7.5/0238

SIMVACOR 40 mg: RSA S4 A39/7.5/0132

9. DATE OF FIRST AUTHORISATION

SIMVACOR 10 mg and SIMVACOR 20 mg: 15 November 2002

SIMVACOR 40 mg: 08 June 2007

10. DATE OF REVISION OF THE TEXT

06 July 2022

SIMVACOR 10 mg: NAM NS2 04/7.5/1660

BOT S2 1202043

SIMVACOR 20 mg: NAM NS2 04/7.5/1659

BOT S2 1202044

MOZ 2885

SIMVACOR 40 mg: NAM NS2 07/7.5/0166

MOZ 2886