PROFESSIONAL INFORMATION FOR SIMVOTIN 10, 20 & 40

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

SIMVOTIN 10 Tablets

SIMVOTIN 20 Tablets

SIMVOTIN 40 Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SIMVOTIN 10 Tablets

Each tablet contains simvastatin (micronised) 10 mg.

SIMVOTIN 20 Tablets

Each tablet contains simvastatin (micronised) 20 mg.

SIMVOTIN 40 Tablets

Each tablet contains simvastatin (micronised) 40 mg.

Contains sugar

SIMVOTIN 10 Tablets contains 72,210 mg

SIMVOTIN 20 Tablets contains 144,420 mg

SIMVOTIN 40 Tablets contains 288,840 mg

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets

SIMVOTIN 10 Tablets: Peach coloured, film-coated, oval shaped tablets debossed with `SST' on one side and `10' on other side with intact coating.

SIMVOTIN 20 Tablets: Tan coloured, film-coated, oval shaped tablets debossed with `SST' on one side and `20' on other side with intact coating.

SIMVOTIN 40 Tablets: Brick red coloured, film-coated, oval shaped tablets debossed with `SST' on one side and `40' on other side with intact coating.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia

SIMVOTIN is indicated, in combination with diet, to decrease elevated serum total cholesterol and LDL-cholesterol in patients with:

- Primary hypercholesterolaemia
- Heterozygous familial hypercholesterolaemia or

- Combined (mixed) hyperlipidaemia when response to diet or other non-pharmacological measures alone are not adequate.

Coronary heart disease

SIMVOTIN 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 for 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

Posology

The patient should be placed on a standard cholesterol-lowering diet before receiving SIMVOTIN and should continue on this diet during treatment with **SIMVOTIN.**

Hypercholesterolaemia

The usual starting dose is 10 mg/day 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 daily given as a single dose in the evening.

If LDL-cholesterol levels fall below 1,94 mmol/l (75 mg/dL) or total plasma cholesterol levels fall below 3,6 mmol/l (140 mg/dL) the dose of **SIMVOTIN** should be reduced.

Coronary Heart Disease

Patients with coronary heart disease can be treated with a starting dose of 20 mg/day given as a single dose in the evening. Dosing adjustments, if required, should be made at intervals of not less than 4 weeks, up to a maximum of 80 mg daily as a single dose in the evening.

Dosage in Renal Insufficiency

SIMVOTIN does not undergo significant renal excretion, therefore, modification of dose~~a~~age should not be necessary in patients with mild to moderate renal insufficiency. In patients with severe renal insufficiency (creatinine clearance < 30 mL/min), dosages above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously.

Concomitant therapy

SIMVOTIN is effective alone or in combination with bile acid sequestrants. When both medicines are prescribed, **SIMVOTIN** should be given 1 hour before or 4 hours after cholestyramine administration.

A maximum daily dosage of 10 mg **SIMVOTIN** is recommended in patients taking ciclosporin, fibrates (other than gemfibrozil) or niacin concomitantly (see section 4.4-Muscle Effects).

The dose should not exceed 20 mg daily in patients receiving concomitant medicines such as amiodarone, verapamil, diltiazem or amlodipine (see section 4.5).

Elderly population

No dosage adjustment is required for this population.

Paediatric population

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

Method of administration

For oral use.

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 diseases.
- Unexplained persistent elevations of serum transaminases.
- Pregnancy and lactation (see section 4.6).
- Concomitant administration of strong CYP3A4 inhibitors (medicines that increase AUC approximately 5-fold or greater) (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, such as ritonavir, saquinavir, nelfinavir, boceprevir and telaprevir; erythromycin, clarithromycin, telithromycin; nefazodone and medicines containing cobicistat) (see sections 4.4 and 4.5).
- In patients with HoFH, concomitant administration of lomitapide with doses > 40 mg **SIMVOTIN** (see section 4.2, section 4.4 and section 4.5)
- Concomitant administration of gemfibrozil, ciclosporin or danazol (see sections 4.4 and 4.5).
- Porphyria: Safety has not been established.

4.4 Special warnings and precautions for use

Myopathy/Rhabdomyolysis

SIMVOTIN, 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 **SIMVOTIN** and simvastatin acid plasma levels), which may be due, in part, to interacting medicines that interfere with **SIMVOTIN** metabolism and/or transporter pathways (see section 4.5).

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related.

The risk of myopathy is greater in patients on simvastatin 80 mg compared with other statin-based therapies with similar LDL-C-lowering efficacy. Therefore, the 80-mg dose of **SIMVOTIN** 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 and when the benefits are expected to outweigh the potential risks. In patients taking simvastatin 80 mg for whom an interacting medicine is needed, a lower dose of simvastatin 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 sections 4.2, 4.3, and 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. 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.

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 x ULN), levels should be re-measured within 5 to 7 days later to confirm the results.

General measures:

All patients starting therapy with **SIMVOTIN** or whose dose of simvastatin is being increased, should be advised of the risk of myopathy and should report, promptly, any unexplained muscle pain, tenderness or weakness. A creatine kinase (CK) level above 10 times the Upper Limit of Normal (ULN) in a patient, with unexplained symptoms, indicates myopathy. **SIMVOTIN** 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 of fibrate.
- Alcohol abuse.

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

Whilst on treatment

If muscle pain, weakness or cramps occur whilst a patient is receiving treatment with a statin, their CK levels should be measured. If these levels are found, in the absence of strenuous

exercise, to be significantly elevated (> 5 x ULN), treatment should be stopped. If muscular symptoms are severe and cause daily discomfort, even if CK levels are < 5 x ULN, treatment discontinuation may be considered. If myopathy is suspected for any other reason, treatment should be discontinued.

There have been very rare reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterised by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment (see 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 **SIMVOTIN** should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

There have been reports of cognitive impairment (such as memory loss, forgetfulness, amnesia and confusion) associated with statins such as **SIMVOTIN**. These were generally not serious, with variable time-to-symptom onset (between 1 day to years) and symptom resolution (median 3 weeks).Increased glycosylated haemoglobin, fasting serum glucose levels and worsening of glycaemic control have been reported with statins such as **SIMVOTIN**.

SIMVOTIN should be used with caution in patients with Type 2 diabetes.

Measures to reduce the risk of myopathy caused by medicine interaction*s (see also section 4.5)*

The risk of myopathy and rhabdomyolysis is significantly increased by concomitant use of **SIMVOTIN** with potent inhibitors of CYP3A4 (such as itraconazole, ketoconazole posaconazole, voriconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, such as ritonavir, saquinavir, nelfinavir, boceprevir and telaprevir; the antidepressant nefazodone, or grapefruit juice, medicine containing cobicistat.

The combined use of **SIMVOTIN** with gemfibrozil, ciclosporin or danazol is contraindicated (see sections 4.3 and 4.5).

In patients receiving cysclosporin, **SIMVOTIN** should be temporarily discontinued if systemic azole derivatives 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 **SIMVOTIN** (see sections 4.2 and 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 **SIMVOTIN**.

Consequently, regarding CYP3A4 inhibitors, the use of **SIMVOTIN** 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 sections 4.3 and 4.5). If treatment with potent CYP3A4 inhibitors (medicines that increase AUC approximately 5-fold or greater)

is unavoidable, therapy with **SIMVOTIN** must be suspended (and use of an alternative statin considered) during the course of treatment. Moreover, caution should be exercised when combining **SIMVOTIN** with certain other less potent CYP3A4 inhibitors: fluconazole, verapamil, diltiazem (see sections 4.2 and 4.5). Concomitant intake of grapefruit juice and simvastatin should be avoided.

The use of **SIMVOTIN** 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 medicine can cause myopathy when given alone.

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

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

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

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

Daptomycin

Cases of myopathy and/or rhabdomyolysis have been reported with HMG-CoA reductase inhibitors (e.g. simvastatin as in **SIMVOTIN**) 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 **SIMVOTIN** 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 **SIMVOTIN**) and for further guidance related to monitoring (see section 4.5).

Hepatic effects

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, **SIMVOTIN** 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 **SIMVOTIN**. If serious liver injury with clinical symptoms and/or hyperbilirubinaemia or jaundice occurs during treatment with **SIMVOTIN**, promptly interrupt therapy. If an alternate aetiology is not found, do not restart **SIMVOTIN**.

SIMVOTIN 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 **SIMVOTIN**. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

Diabetes mellitus

Some evidence suggests that statins as a class raise blood glucose and, in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate.

This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5,6 to 6,9 mmol/L, BMI > 30 kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Interstitial lung disease

Cases of interstitial lung disease have been reported with some statins, including simvastatin, especially with long term therapy (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.

Surgery

Therapy with **SIMVOTIN** should be temporarily stopped a few days prior to elective surgery and when any major medical or surgical condition supervenes.

Chinese patients

Because of an increased risk for myopathy in Chinese patients taking simvastatin 40 mg co-administered with lipid-modifying (greater than or equal to 1 g/day niacin) of niacin-containing products, caution should be used when treating Chinese patients with **SIMVOTIN** doses exceeding 20 mg/day co-administered with lipid-modifying doses of niacin-containing medicines.

Lactose warning

SIMVOTIN contains lactose which may have an effect on the glycaemic control of patients with diabetes_mellitus. Patients with the rare hereditary problems of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **SIMVOTIN**.

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 **SIMVOTIN** 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 **SIMVOTIN** 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 and rhabdomyolysis is increased during concomitant administration with fibrates. Additionally, there is a pharmacokinetic interaction with gemfibrozil resulting in increased **SIMVOTIN** plasma levels (see below Pharmacokinetic interactions and sections 4.3 and 4.4). When **SIMVOTIN** 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 **SIMVOTIN** 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 **SIMVOTIN**
Other fibrates (except fenofibrate)	Do not exceed 10 mg **SIMVOTIN** daily
Fusidic acid	Is not recommended with **SIMVOTIN**
Niacin (nicotinic acid) (≥ 1 g/day)	For Asian patients, not recommended with **SIMVOTIN**
Amiodarone Amlodipine Verapamil Diltiazem Elbasvir	Do not exceed 20 mg **SIMVOTIN** daily

Grazoprevir	
Lomitapide	For patients with HoFH, do not exceed 40 mg **SIMVOTIN** daily
Daptomycin	It should be considered to temporarily suspend **SIMVOTIN** in patients taking daptomycin unless the benefits of concomitant administration outweigh the risk (see section 4.4)
Ticagrelor	Doses greater than 40 mg **SIMVOTIN** daily are not recommended
Grapefruit juice	Avoid grapefruit juice when taking **SIMVOTIN**

Effects of other medicines on SIMVOTIN

Interactions involving inhibitors of CYP3A4

SIMVOTIN 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 **SIMVOTIN** 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 **SIMVOTIN** must be suspended (and use of an alternative statin considered) during the course of treatment. Caution should be exercised when combining **SIMVOTIN** 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 simvastatin (such as **SIMVOTIN**) and fluconazole have been reported (see section 4.4).

Ciclosporin

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ciclosporin with **SIMVOTIN**; therefore, use with ciclosporin is contraindicated (see sections 4.3 and 4.4). Although the mechanism is not fully understood, ciclosporin has been shown to increase the AUC of HMG-CoA reductase inhibitors such as **SIMVOTIN**. The increase in AUC for simvastatin such as in **SIMVOTIN** 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 **SIMVOTIN**; therefore, use with danazol is contraindicated (see sections 4.3 and 4.4).

Gemfibrozil

Gemfibrozil increases the AUC of simvastatin by 1,9-fold, possibly due to inhibition of the glucuronidation pathway and/or OATP1B1 (see sections 4.3 and 4.4). Concomitant administration of **SIMVOTIN** with gemfibrozil is contraindicated (see section 4.4).

A maximum dose of 10 mg **SIMVOTIN** daily is recommended in patients taking fibrates (other than gemfibrozil) or lipid-lowering doses of niacin (nicotinic acid).

Fusidic acid

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins (such as **SIMVOTIN**). Co-administration of this combination may cause increased plasma concentrations of both medicines. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with fusidic acid is necessary, **SIMVOTIN** 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 **SIMVOTIN** (see section 4.4). The dose of **SIMVOTIN** 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 **SIMVOTIN** 40 mg or 80 mg (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 **SIMVOTIN** 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 **SIMVOTIN** 80 mg (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 **SIMVOTIN** should not exceed 20 mg daily in patients receiving concomitant medication with diltiazem.

- *Amlodipine*

Patients on amlodipine treated concomitantly with **SIMVOTIN** 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 **SIMVOTIN** 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 **SIMVOTIN** (see sections 4.3 and 4.4). Therefore, in patients with HoFH, the dose of **SIMVOTIN** 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 **SIMVOTIN**, particularly at higher doses, may have an increased risk of myopathy (see section 4.4).

Niacin (nicotinic acid)

Rare cases of myopathy/rhabdomyolysis has 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 **SIMVOTIN** 20 mg resulted in a modest increase in the AUC of **SIMVOTIN** and simvastatin acid and in the C_{max} of simvastatin acid plasma concentrations.

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 **SIMVOTIN** and an increased risk of myopathy (see section 4.4).

Ticagrelor:

Co-administration of ticagrelor with **SIMVOTIN** increased **SIMVOTIN** C_{max} by 81 % and AUC by 56 % and increased simvastatin acid C_{max} by 64 % and AUC by 52 % with some individual increases equal to 2 to 3 fold. Co-administration of ticagrelor with doses of **SIMVOTIN** exceeding 40 mg daily could cause adverse reactions of simvastatin and should be weighed against potential benefits. There was no effect of simvastatin on ticagrelor plasma levels. The concomitant use of ticagrelor with doses of **SIMVOTIN** greater than 40 mg is not recommended.

Colchicine

There have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and **SIMVOTIN** 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 **SIMVOTIN**. 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.

Daptomycin:

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

*Effects of **SIMVOTIN** on the pharmacokinetics of other medicines:*

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

Caution should be exercised in the concomitant use of **SIMVOTIN** with ciclosporine, itraconazole, ketoconazole, fibric acid derivatives, niacin, erythromycin, clarithromycin, HIV protease inhibitors or nefazodone (see 4.4 - Skeletal Muscle).

Digoxin

SIMVOTIN may cause increases in digoxin levels.

Warfarin

A possible increase in the anticoagulant effect of the warfarin may occur. Patients taking warfarin should have their INR determined before starting **SIMVOTIN** therapy. The INR should be monitored frequently enough in the early stages of therapy until stabilised. Once a stable

prothrombin time has been documented, INR can be monitored at the intervals usually recommended for patients on warfarin. When there is a dose adjustment of **SIMVOTIN**, this procedure should be repeated. **SIMVOTIN** therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Bile acid sequestrants

Caution should be exercised in the concomitant use of fibric acid derivatives and niacin.

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

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 **SIMVOTIN** should therefore be avoided.

Propranolol

The pharmacokinetics of the enantiomers of propranolol was not affected with concomitant administration of single dose **SIMVOTIN** and propranolol.

4.6 Fertility, pregnancy and lactation

The active metabolite of ARROW SIMVASTATIN is fetotoxic and teratogenic in rats and it should therefor not be used in female patients of childbearing potential.

Pregnancy

SIMVOTIN is contraindicated during pregnancy (see section 4.3).

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

Although there is no evidence that the incidence of congenital anomalies in offspring of patients taking **SIMVOTIN** or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with **SIMVOTIN** 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, **SIMVOTIN** must not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant.

Treatment with **SIMVOTIN** must be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see sections 4.3 and 5.3).

Breastfeeding

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

Fertility

No clinical trial data are available on the effects of **SIMVOTIN** on human fertility. **SIMVOTIN** had no effect on the fertility of male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

SIMVOTIN 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

Tabulated list of adverse reactions

MedDRA System Organ Class	**Frequency**	**Adverse reaction**
Blood and lymphatic system disorders	*Less frequent*	Anaemia, thrombocytopenia, increased erythrocyte sedimentation rate, eosinophilia.
	Frequency unknown	Neutropenia.
Immune system disorders	*Less frequent*	Anaphylaxis, reactions may include angioedema,lupus-like syndrome, toxic epidermal necrosis, erythema multiforme, including Stevens-Johnson syndrome.
Endocrine disorders	*Less frequent*	Increases in HbA1C and fasting glucose levels. Diabetes mellitus.

Metabolism and nutrition disorders	*Frequency unknown*	Mass gain has been reported.
Psychiatric disorders	*Less frequent*	Insomnia
	Frequency unknown	Depression, sleep disturbances (including nightmares)
Nervous system disorders	*Less frequent*	Dizziness, headache, paraesthesia, peripheral neuropathy, cognitive impairment such as memory loss, forgetfulness, amnesia, confusion.
Eye disorders	*Less frequent*	Photosensitivity, vision blurred, visual impairment.
Cardiac disorders	*Less frequent*	Atrial fibrillation
Vascular disorders	*Less frequent*	Vasculitis.
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Dyspnoea, hypersensitivity pneumonitis
	Frequency unknown	Interstitial lung disease (see section 4.4), respiratory infections, bronchitis, sinusitis.
Gastro-intestinal disorders	*Less frequent*	Constipation, diarrhoea, nausea, flatulence, dyspepsia, abdominal pain, cramps, vomiting, pancreatitis, gastritis
Hepato-biliary disorders	*Less frequent*	Hepatitis/jaundice, fatal and non-fatal hepatic failure.
Skin and subcutaneous tissue disorders	*Less frequent*	Skin rash, pruritus, alopecia, eczema, urticaria, lichenoid medicine eruptions.

Musculoskeletal and connective tissue disorders	*Less frequent*	Myalgia, muscle cramps, myopathy (including myositis), arthralgia, rhabdomyolysis (presenting as muscle pain with elevated creatine phosphokinase and myoglobinuria leading to renal failure), muscle rupture, polymyalgia, rheumatic, arthritis, arthralgia.
	Frequency unknown	tendinopathy, sometimes complicated by rupture, immune-mediated necrotising myopathy (IMNM) **.
Reproductive system and breast disorders	*Less frequent*	Gynecomastia
	Frequency unknown	Erectile dysfunction.
General disorders and administration site condition	*Less frequent*	Asthenia***, oedema, swelling, fever, flushing, malaise
	Frenquency unknown	Fatigue
Investigations	*Less frequent:*	Marked and persistent increases of serum transaminases (alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transpeptidase) see section 4.4 Hepatic effects), and elevated alkaline phosphatase. Liver function test abnormalities. Increases in serum creatine kinase (CK) levels derived from skeletal muscle (see section 4.4).

Laboratory Test Findings

Marked and persistent increases of serum transaminases have been reported infrequently. 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).

The following additional adverse events have been reported with some statins:

- Sleep disturbance
- Sexual dysfunction
- Diabetes mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5,6 mmol/L, BMI > 30kg/m^2, raised triglycerides, history of hypertension).

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 characterized

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).

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

Paediatric population

The long-term effects on physical, intellectual, and sexual maturation are unknown.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the '6.04 Adverse Drug Reaction Reporting form', found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/index/8

4.9 Overdose

(See sections 4.4 and 4.8). General measures should be adopted and liver function should be monitored. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological Classification

A 7.5 Serum-cholestrol reducers.

Pharmacotherapeutic group: HMG-CoA reductase inhibitor

ATC-Code: C10A A01

5.1 Pharmacodynamic properties

Simvastatin is a cholesterol-lowering medicine derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion simvastatin, which is an inactive lactone, is hydrolysed in the liver to the corresponding beta-hydroxy acid, the active form. This is the principal metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early 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. As a result of these changes the ratios of total- to HDL-C and LDL- to HDL-C are reduced.

5.2 Pharmacokinetic properties

Simvastatin is an inactive lactone which is readily hydrolysed in vivo to the corresponding beta-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Hydrolysis takes place mainly in the liver; the rate of hydrolysis in human plasma is very slow.

The pharmacokinetic properties have been evaluated in adults. Pharmacokinetic data in children and adolescents are not available**.**

- **Absorption:** In man simvastatin is well absorbed and undergoes extensive hepatic first-pass extraction. The extraction in the liver is dependent on the hepatic blood flow. The liver is the primary site of action of the active form. The availability of the beta-hydroxyacid to the systemic circulation following an oral dose of simvastatin was found to be less than 5 % of the dose. Maximum plasma concentration of active inhibitors is reached approximately 1-2 hours after administration of simvastatin. Concomitant food intake does

not affect the absorption.

The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of medicine occurred after multiple dosing.

- **Distribution:** 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.

- **Elimination:** Simvastatin is a substrate of CYP3A4 (see sections 4.3 and 4.5). 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 medicine equivalents excreted in bile as well as unabsorbed medicine. Following an intravenous injection of the beta-hydroxyacid metabolite, its half-life averaged 1,9 hours. An average of only 0,3 % of the IV dose was excreted in urine as inhibitors.

  Simvastatin acid is taken up actively into the hepatocytes by the transporter OATP1B1.

  Simvastatin is a substrate of the efflux transporter BCRP.

Special Populations

SLCO1B1 polymorphism

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

exposure of simvastatin acid, which may lead to an increased risk of rhabdomyolysis (see section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Pregelatinised starch

Ascorbic acid

Citric acid monohydrate

Cellulose microcrystalline (PH 101)

Water purified

Butylated hydroxyl anisole (BHA)

Isopropyl alcohol

Croscarmellose sodium,

Magnesium stearate

Film-coating

- Hydroxypropyl cellulose
- Hypromellose 15Cp
- Titanium dioxide (C.L No.77891)
- Talc
- Iron oxide red (C.L No. 77491)

- Iron oxide black (C.L No. 77499)
- Iron oxide yellow (C.L No. 77492)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C, protected from light and moisture.

Do not remove the blister from the carton until required for use.

KEEP PUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

28, 30 or 100 tablets packed in PVC/PVdC blister strips.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill Ext.1

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER(S)

SIMVOTIN 10 Tablets**: 36/7.5/0373**

SIMVOTIN 20 Tablets: **36/7.5/0374**

SIMVOTIN 40 Tablets: **36/7.5/0375**

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 May 2004

10. DATE OF REVISON OF THE TEXT

03 May 2023

Namibia: NS2 Reg.No.:

Simvotin 10 Tablets: 05/7.5/0218

Simvotin 20 Tablets: 05/7.5/0219

Simvotin 40 Tablets: 05/7.5/0220