Professional Information (PI) for Medicines for Human Use

UNISIM (film-coated tablets)

SCHEDULING STATUS S4

1 NAME OF THE MEDICINE

UNISIM 10 (film-coated tablets)

UNISIM 20 (film-coated tablets)

UNISIM 40 (film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

UNISIM 10

Each film-coated tablet contains simvastatin (micronised) 10 mg.

Contains sugar: Lactose monohydrate 72,21 mg per tablet.

Also contains:

Butylated hydroxyanisole NMT 0,0389 % *m/m* (antioxidant)

Ascorbic acid NMT 2,676 % *m/m* (antioxidant synergist)

Citric acid monohydrate NMT 1,338 % *m/m* (sequesterant)

UNISIM 20

Each film-coated tablet contains simvastatin (micronised) 20 mg.

Contains sugar: Lactose monohydrate 144,42 mg per tablet.

Also contains:

Butylated hydroxyanisole NMT 0,0389 % *m/m* (antioxidant)

Ascorbic acid NMT 2,676 % *m/m* (antioxidant synergist)

Citric acid monohydrate NMT 1,338 % *m/m* (sequesterant)

UNISIM 40

Each film-coated tablet contains simvastatin (micronised) 40 mg.

Contains sugar: Lactose monohydrate 288,84 mg per tablet.

Also contains:

Butylated hydroxyanisole NMT 0,0389 % *m/m* (antioxidant)

Ascorbic acid NMT 2,676 % *m/m* (antioxidant synergist)

Citric acid monohydrate NMT 1,338 % *m/m* (sequesterant)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

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

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

UNISIM 40: 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

UNISIM 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 are not adequate.

Coronary heart disease

UNISIM 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 must follow a cholesterol-lowering diet before initiation of, and while on **UNISIM** therapy.

Hypercholesterolaemia

Adults

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

The dose of **UNISIM** 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.

Dosage in Renal Insufficiency

UNISIM 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 < 30 mℓ/min), dosages above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously.

Concomitant therapy

UNISIM is effective alone or in combination with bile acid sequestrants. When both medicines are prescribed, **UNISIM** should be given 1 hour before or 4 hours after cholestyramine administration (see section 4.5).

A maximum daily dose of 10 mg **UNISIM** is recommended in patients taking ciclosporin, fibrates (other than gemfibrozil) or niacin concomitantly (see section 4.3 and section 4.5).

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

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

4.3 Contraindications

- Hypersensitivity to simvastatin, other HMG-CoA reductase inhibitors or any of the excipients of **UNISIM** 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 potent CYP3A4 inhibitors (medicines that increase AUC approximately 5-fold or greater) (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors (e.g. ritonavir, saquinavir and nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone and medicines containing cobicistat) (see section 4.4 and section 4.5).
- Concomitant administration of gemfibrozil, ciclosporin or danazol (see section 4.4 and section 4.5).
- Porphyria: Safety has not been established.
- In patients with HoFH, concomitant administration of lomitapide with doses > 40 mg **UNISIM** (See section 4.4 and section 4.5).

4.4 Special warnings and precautions for use

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

Muscle Effects

Risk of myasthenia gravis and ocular myasthenia.

UNISIM 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 **UNISIM** and simvastatin acid plasma levels), which may be due, in part, to interacting medicines that interfere with **UNISIM** metabolism and/or transporter pathways (see 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. ciclosporin) or in patients who are carriers of the SLCO1B1 c.521T>C genotype.

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:

Patients starting therapy with **UNISIM** should be advised of the risk of myopathy and should report, promptly, 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. **UNISIM** 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 necrotizing myopathy (IMNM) during or after treatment with some statins. INMN is clinically characterized 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.

Measures to reduce the risk of myopathy caused by medicine interactions:

The benefit and risks of using **UNISIM** concomitantly with immune-suppressants, fibrates

(except fenofibrate) or lipid lowering doses of niacin should be carefully considered, and the dose of **UNISIM** should generally not exceed 10 mg/day.

Cautions should be used when prescribing fenofibrate with **UNISIM**, as either medicine can cause myopathy when given alone.

The risk of myopathy and rhabdomyolysis is increased by high levels of **UNISIM** activity in plasma. Simvastatin is metabolised by the cytochrome P450 isoform 3A4. Certain medicines which inhibit this metabolic pathway can raise the plasma levels of simvastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole posaconazole, voriconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors (e.g. ritonavir, saquinavir and nelfinavir), boceprevir, telaprevir, the antidepressant nefazodone and medicines containing cobicistat. Combination of these medicines with **UNISIM** is contraindicated. If short-term treatment with potent CYP3A4 inhibitors (medicines that increase AUC approximately 5-fold or greater) is unavoidable, therapy with **UNISIM** must be suspended (and use of an alternative statin considered) during the course of treatment.

Moreover, caution should be exercised when combining **UNISIM** with certain other less potent CYP3A4 inhibitors: fluconazole, verapamil, diltiazem (see section 4.2 and section 4.5).

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

Concomitant intake of grapefruit juice and **UNISIM** should be avoided.

The risk of myopathy and rhabdomyolysis is also increased by concomitant use of amiodarone, amlodipine, verapamil, or diltiazem with certain doses of **UNISIM** (see section 4.2 and section 4.5). The risk of myopathy, including rhabdomyolysis, may be increased by

concomitant administration of fusidic acid with statins (see section 4.5). For patients with HoFH, this risk may be increased by concomitant use of lomitapide with **UNISIM**.

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

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

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

UNISIM is recommended (see section 4.2).

Simvastatin as in **UNISIM** 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 **UNISIM** and an increased risk of myopathy; therefore, a dose adjustment of **UNISIM** should be considered depending on the prescribed dose. Co-administration of elbasvir and grazoprevir with **UNISIM** has not been studied; however, the dose of **UNISIM** should not exceed 20 mg daily in patients receiving concomitant treatment with medicines containing elbasviror 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 **UNISIM**) 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 **UNISIM** 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 **UNISIM)** and for further guidance related to monitoring (see section 4.5).

Diabetes mellitus

Increase in HbA1C and fasting blood glucose levels have been reported with statin use, including **UNISIM**. In some patients, at high risk of future diabetes, **UNISIM** 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.

UNISIM 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 **UNISIM** therapy and periodically until one year after the last elevation in dose. 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 those patients, measurements should be repeated promptly and then performed more frequently. **UNISIM** 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). 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 **UNISIM** may occur. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with **UNISIM**, promptly interrupt therapy. If an alternate aetiology is not found, do not restart **UNISIM**.

UNISIM should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of **UNISIM.**

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

Surgery

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

Chinese patients

Because the incidence of myopathy is higher in Chinese than in non-Chinese patients, co-administration of simvastatin with lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid) is

not recommended in Asian patients.

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.

Lactose

UNISIM contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take **UNISIM.**

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 **UNISIM** 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 **UNISIM** 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 **UNISIM** plasma levels (see below Pharmacokinetic interactions and section 4.3 and section 4.4). When **UNISIM** 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 **UNISIM** 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 Ciclosporin Danazol Gemfibrozil	Contraindicated with **UNISIM**
Other fibrates (except fenofibrate)	Do not exceed 10 mg **UNISIM** daily
Fusidic acid	It is not recommended with **UNISIM**
Niacin (nicotinic acid) (≥ 1 g/day)	For Asian patients, not recommended with **UNISIM**
Amiodarone Amlodipine Verapamil	Do not exceed 20 mg **UNISIM** daily

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

Effects of other medicines on UNISIM

Interactions involving inhibitors of CYP3A4

UNISIM 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 **UNISIM** therapy. Such inhibitors include itraconazole, ketoconazole, posaconazole, voriconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors (e.g. ritonavir, saquinavir and nelfinavir), boceprevir, telaprevir, the antidepressant nefazodone, or grapefruit juice and medicines containing cobicistat. Combination of these medicines with **UNISIM** is contraindicated.

If short-term treatment with potent CYP3A4 inhibitors (medicines that increase AUC approximately 5-fold or greater) is unavoidable, therapy with **UNISIM** must be suspended (and use of an alternative statin considered) during the course of treatment.

Caution should be exercised when combining **UNISIM** with certain other less potent CYP3A4 inhibitors: fluconazole, verapamil, diltiazem (see section 4.2 and section 4.5).

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

Fluconazole

Cases of rhabdomyolysis associated with concomitant administration of simvastatin (such as **UNISIM**) and fluconazole have been reported (see section 4.4).

Ciclosporin

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

A maximum dose of 10 mg **UNISIM** 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 **UNISIM**). 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, **UNISIM** 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 **UNISIM** see section 4.4). The dose of **UNISIM** should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone.

Calcium Channel Blockers

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of **UNISIM** with calcium channel blockers verapamil, diltiazem and amlodipine (see ~~**AND**~~ section 4.4). Concomitant administration with calcium channel blockers results in an increase in

exposure of simvastatin acid (diltiazem 2,7 fold, amlodipine 1,6 fold, verapamil 2,3 fold), presumably due to inhibition of CYP3A4. Therefore, the dose of **UNISIM** should not exceed 20 mg daily in patients receiving concomitant medication with calcium channel blockers.

Lomitapide

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

Moderate Inhibitors of CYP3A4

Patients taking other medicines having a moderate inhibitory effect on CYP3A4 concomitantly with **UNISIM**, particularly at higher 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 **UNISIM** and an increased risk of myopathy (see section 4.4).

Niacin (nicotinic acid)

Myopathy/rhabdomyolysis has been associated with simvastatin co-administered with lipid-modifying doses (≥ 1 g/day) of niacin (nicotinic acid).

Ticagrelor

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

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 **UNISIM** should therefore be avoided.

Colchicine

There have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and **UNISIM** in patients with renal insufficiency. 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. **UNISIM**) 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 **UNISIM**. 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.

Digoxin

UNISIM may cause increases in digoxin levels.

Effects of UNISIM on the pharmacokinetics of other medicinal products

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

Warfarin

A possible increase in the anticoagulant effect of the warfarin may occur. Patients taking warfarin should have their INR determined before starting **UNISIM** 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 **UNISIM**, this procedure should be repeated.

Bile acid sequestrants

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

Propranolol

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

4.6 Fertility, pregnancy and lactation

UNISIM is contraindicated in pregnancy and lactation (see section 4.3).

Women of childbearing potential

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

Pregnancy:

Safety in pregnancy has not been established. No controlled clinical trials with **UNISIM** 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 **UNISIM** 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, **UNISIM** must not be used in women who are pregnant, trying to become pregnant or suspect they are

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

Breastfeeding

It is not known whether **UNISIM** 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 **UNISIM** must not breastfeed their babies (see section 4.3).

Fertility

No clinical trial data are available on the effects of **UNISIM** on human fertility.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines, it should be taken into account that dizziness has been reported.

4.8 Undesirable effects

Table 1: Tabulated list of adverse reactions

System Organ Class	Adverse reactions	Frequency
Blood and lymphatic system disorders	Anaemia, neutropenia.	*Less frequent*
Immune system disorders	An apparent hypersensitivity syndrome has been reported. Reactions may include angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis,	*Less frequent*

	thrombocytopenia, increased erythrocyte sedimentation rate (ESR), eosinophilia, arthritis, arthralgia, urticaria, photosensitivity, fever, flushing, malaise, dyspnoea, toxic epidermal necrosis, erythema multiforme, including Stevens-Johnson syndrome. Anaphylaxis.	
Endocrine disorders	Increases in HbA1C and fasting glucose levels. Diabetes mellitus.	*Less Frequent*
Metabolism and nutritional disorders	Mass gain has been reported.	*Frequency unknown*
Psychiatric disorders	Insomnia.	*Less frequent*
	Depression, sleep disturbances (including nightmares).	*Frequency unknown*
Nervous system disorders	Dizziness, headache, paraesthesia, peripheral neuropathy, fatigue. Cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion).	*Less frequent*
	Myasthenia gravis.	*Frequency unknown*
Cardiac disorders	Atrial fibrillation.	*Less frequent*
Eye disorders	Photosensitivity, vision blurred, visual	*Less frequent*

	impairment.	
	Ocular myasthenia.	*Frequency unknown*
Respiratory, thoracic and mediastinal disorders	Dyspnoea, hypersensitivity pneumonitis.	*Less frequent*
	Interstitial lung disease (see section 4.4), respiratory infections, bronchitis, sinusitis.	*Frequency unknown*
Gastrointestinal disorders	Nausea, flatulence, dyspepsia, abdominal pain, cramps, vomiting.	Frequent
	Constipation, diarrhoea, pancreatitis, gastritis.	Less Frequent
Hepatobiliary disorders	Hepatitis/jaundice, fatal and non-fatal hepatic failure.	*Less frequent*
Skin and subcutaneous tissue disorders	Skin rash, pruritus, alopecia, eczema. Lichenoid drug eruptions.	*Less frequent*
Musculoskeletal and connective tissue disorders	Myalgia, muscle cramps.	*Frequent*
	Mopathy, myositis, arthralgia, rhabdomyolysis (presenting as muscle pain with elevated creatine phosphokinase and myoglobinuria leading to renal failure), muscle rupture.	*Less Frequent*
	Tendinopathy; sometimes complicated by rupture,	*Frequency unknown*

	immune-mediated necrotising myopathy (IMNM)**.	
Reproductive system and breast disorders	Gynecomastia.	*Less Frequent*
	Erectile dysfunction.	*Frequency unknown*
General disorders and administration site conditions	Asthenia, oedema, swelling.	*Less Frequent*
Investigations	Marked and persistent increases of serum transaminases and elevated alkaline phosphatase and gamma-glutamyl transpeptidase. Liver function test abnormalities. Increases in serum creatine kinase (CK) levels derived from skeletal muscle (see section 4.4)	*Less frequent*

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

• Sexual dysfunction

Paediatric population

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

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).

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 Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A 7.5 Serum-cholesterol reducers.

ATC-code: C10A A01

Simvastatin is a cholesterol-lowering agent derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion simvastatin, an inactive lactone, is hydrolysed to the beta-hydroxyacid, 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 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 %.

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 excreted primarily via the liver and less than 13 % of its metabolites are excreted in the urine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Ascorbic acid

Butylated hydroxyanisole

Citric acid monohydrate

Croscarmellose sodium

Isopropyl alcohol

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Pregelatinised starch

Tablet coating:

Hydroxypropyl cellulose (E463)

Hypromellose (E464)

Iron oxide black (E172)

Iron oxide red (E172)

Iron oxide yellow (E172)

Talc (E553 b)

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C, protected from light and moisture. Do not remove the blisters from the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Cartons containing 28, 30 or 100 tablets packed in PVdC coated PVC blister strips.

6.6 Special precautions for disposal

Not applicable.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Unimed Healthcare (Pty) Ltd

Corner Birch Road & Bluegum Avenue

Anchorville

Lenasia, 1827

South Africa

8 REGISTRATION NUMBERS

UNISIM 10: 36/7.5/0370

UNISIM 20: 36/7.5/0371

UNISIM 40*:* 36/7.5/0372

9 DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

28 May 2005

10 DATE OF REVISION OF THE TEXT

22 June 2023