APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

ROLTESIM 40 (Film-coated tablets)

ROLTESIM 80 (Film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ROLTESIM 40: Each film-coated tablet contains 40 mg simvastatin

ROLTESIM 80: Each film-coated tablet contains 80 mg simvastatin

Contains sugar:

ROLTESIM 40: Lactose monohydrate 270,80 mg

ROLTESIM 80: Lactose monohydrate 541,60 mg.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

ROLTESIM 40: Pink-coloured, oval, biconvex, intact, film-coated tablets debossed with ‘SVN 40’ on one side and plain on the other side.

ROLTESIM 80: Pink-coloured, capsule-shaped, biconvex, intact, film-coated tablets debossed with ‘SVN 80’ on one side and scored on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia:

ROLTESIM 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:

ROLTESIM 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); 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 **ROLTESIM** therapy.

Hypercholesterolaemia:

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

The dose of **ROLTESIM** 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 40 mg daily as a single dose in the evening (see section 4.4).

Special populations

Renal insufficiency:

ROLTESIM 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, **ROLTESIM** therapy should be closely monitored and doses above 10 mg/day should be implemented with caution.

Concomitant therapy:

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

hours after cholestyramine administration (see section 4.5). A maximum daily dose of 10 mg **ROLTESIM** is recommended in patients taking ciclosporin, fibrates or niacin concomitantly (see section 4.5).

Paediatric population

The safety and efficacy of **ROLTESIM** have not been established in paediatric patients (see section 4.4).

Method of administration

The tablet should be swallowed whole.

ROLTESIM 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 ingredients in **ROLTESIM**.
- Acute or chronic liver disease.
- Unexplained persistent elevations of serum transaminases.
- Pregnancy and lactation (see section 4.4 and 4.6).
- Porphyria: Safety has not been established.
- Concomitant administration of strong CYP3A4 inhibitors, e.g. itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin, and nefazodone (see section 4.5).
- Concomitant administration of gemfibrozil, ciclosporin or danazol (see section 4.5.

4.4 Special warnings and precautions for use

The active metabolite of **ROLTESIM** is foetotoxic and teratogenic in rats, and it should therefore not be used in female patients of child-bearing potential (see section 4.3 and 4.6).

ROLTESIM less frequently causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal. Myopathy sometimes takes the form of rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, and fatalities have occurred. The risk of myopathy is increased by high levels of statin activity in plasma. Predisposing factors for myopathy include advanced age (≥ 65 years), female gender, uncontrolled hypothyroidism, and renal impairment.

The risk of myopathy, including rhabdomyolysis, is dose related. The risk of myopathy, including rhabdomyolysis, is greater in patients on ROLTESIM 80, compared with other statin therapies with similar or greater LDL-C lowering efficacy and compared with lower doses of simvastatin. Therefore, the 80 mg dose of ROLTESIM should be used only in patients who have been taking simvastatin 80 mg chronically (e.g. for 12 months or more) without evidence of muscle toxicity (see section 4.2). If, however, a patient who is currently tolerating the 80 mg dose of ROLTESIM needs to be initiated on an interacting medicine that is contra-indicated (see section 4.3) or is associated with a dose cap for simvastatin, that patient should be switched to an alternative statin with less potential for this medicine interaction. Patients should be advised of the increased risk of myopathy, including rhabdomyolysis, and to report promptly any unexplained muscle pain, tenderness or weakness. If symptoms occur, treatment should be discontinued immediately.

All patients starting therapy with ROLTESIM, or whose dose of ROLTESIM is being increased, should be advised of the risk of myopathy, including rhabdomyolysis, and told to report promptly any unexplained muscle pain, tenderness or weakness. ROLTESIM therapy should be discontinued immediately if myopathy is diagnosed or suspected. In most cases, muscle symptoms and creatine kinase (CK) increases resolved when treatment was promptly discontinued. Periodic CK determinations may be considered in patients starting therapy with **ROLTESIM** or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy (refer to “Reducing the risk of Myopathy” below).

Many of the patients who have developed rhabdomyolysis on therapy with simvastatin, as in **ROLTESIM**, have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. **ROLTESIM** therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected. **ROLTESIM** therapy should also be temporarily withheld in any patients experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g. sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine, or electrolyte disorders, or uncontrolled epilepsy.

Persistent increases (to more than 3 x the Upper Limit of Normal – ULN) in serum transaminases have occurred in patients who received simvastatin, as in ROLTESIM. When treatment was discontinued or interrupted in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases

were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

It is recommended that liver function tests be performed before the initiation of treatment, and thereafter when clinically indicated. There have been post-marketing reports of fatal and non-fatal hepatic failure in patients taking statins, including **ROLTESIM**. If serious liver injury with clinical symptoms and/or hyperbilirubinaemia or jaundice occurs during treatment with **ROLTESIM**, promptly interrupt therapy. If an alternate aetiology is not found, do not restart **ROLTESIM**. Note that alanine aminotransferase (ALT) may emanate from muscle, therefore ALT rising with CK may indicate myopathy.

Moderate (< 3 x ULN) elevations of serum transaminases have been reported following therapy with **ROLTESIM**. These changes appeared soon after initiation of therapy with simvastatin, including **ROLTESIM**, were often transient, were not accompanied by any symptoms and did not require interruption of treatment.

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including **ROLTESIM**.

ROLTESIM 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 **ROLTESIM** therapy and periodically, until one year after the last elevation in dose. **ROLTESIM** 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:

Reducing the risk of myopathy:

1. General measures:

   Patients starting therapy with **ROLTESIM** 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. **ROLTESIM** should be discontinued if myopathy is diagnosed or suspected.

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

   The benefits and risks of using **ROLTESIM** concomitantly with immunosuppressants, fibrates or lipid-lowering doses of niacin should be carefully considered, and the dose of **ROLTESIM** should generally not exceed 10 mg/day. Concomitant administration with ciclosporin,

itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, HIV-protease inhibitors and nefazodone, is contra-indicated (see section 4.3 and 4.5).

Lactose:

ROLTESIM tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take **ROLTESIM**.

Paediatric population

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

4.5 Interaction with other medicines and other forms of interaction

Myopathy caused by medicine interactions:

Concomitant administration of medicines that inhibit cytochrome P450 isoenzyme CYP3A4 may result in high plasma levels of **ROLTESIM**, thus increasing the risk of myopathy, and is contra-indicated (see section 4.3). Medicines that inhibit cytochrome P450 isoenzyme CYP3A4 include ciclosporin, itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV-protease inhibitors, nefazodone, or large quantities of grapefruit juice (> 1 ℓ daily). If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, or telithromycin is unavoidable, therapy with **ROLTESIM** must be suspended during the course of treatment.

In vitro studies have demonstrated a potential for voriconazole to inhibit the metabolism of simvastatin. Adjustment of the **ROLTESIM** dose may be needed to

reduce the risk of myopathy, including rhabdomyolysis, if voriconazole must be used concomitantly with **ROLTESIM**.

The combined use of **ROLTESIM** with gemfibrozil, ciclosporin, or danazol is contra-indicated (see section 4.3).

The risk of myopathy is increased when other medicines that cause myopathy, such as fibrates and niacin, are given with **ROLTESIM**. A maximum dose of 10 mg **ROLTESIM** daily is recommended in patients taking other fibrates or lipid-lowering doses of niacin (nicotinic acid). The benefits of the combined use of **ROLTESIM** with the following medicines should be carefully weighed against the potential risks of combinations: amiodarone, verapamil, diltiazem, or amlodipine (see Table 1).

Table 1: Medicine interactions associated with increased risk of myopathy/rhabdomyolysis:

Interacting medicines	**Prescribing recommendations**
Strong CYP3A4 inhibitors, e.g.: Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telithromycin	Contra-indicated with **ROLTESIM**.

HIV protease inhibitors Nefazodone Gemfibrozil Ciclosporin Danazol	
Verapamil Diltiazem	Do not exceed 10 mg **ROLTESIM** daily.
Amiodarone Amlodipine	Do not exceed 20 mg **ROLTESIM** daily.
Grapefruit juice	Avoid large quantities of grapefruit juice (> 1 ℓ daily).

Colchicine:

Cases of myopathy, including rhabdomyolysis have been reported with simvastatin, as in **ROLTESIM**, coadministered with colchicine, and caution should be exercised when prescribing **ROLTESIM** with colchicine.

Digoxin:

ROLTESIM may cause increases in digoxin levels.

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 determined

before starting **ROLTESIM** 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 **ROLTESIM**, this procedure should be repeated.

Bile acid sequestrants:

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

The active metabolite of **ROLTESIM** is foetotoxic and teratogenic in rats, and it should therefore not be used in female patients of child-bearing potential (see section 4.3 and 4.4).

Pregnancy

Safety in pregnancy has not been established.

Breastfeeding

Safety in breastfeeding has not been established.

4.7 Effects on ability to drive and use machines

ROLTESIM may cause dizziness or vertigo. Therefore, patients should be advised not to drive or operate machinery until individual susceptibility is known.

4.8 Undesirable effects

a. Summary of the safety profile

Not applicable

b. Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequent	Upper respiratory tract infection, urinary tract infection
Blood and lymphatic system disorders	Frequent	Anaemia, neutropenia (see **"Immune system disorders"**)
Immune system disorders	Less frequent	Reactions may include angioedema, lupus-like syndrome, polymyalgia rheumatica, vasculitis, thrombocytopenia, increased erythrocyte sedimentation rate, eosinophilia, arthritis, arthralgia, urticaria, photosensitivity, fever, flushing, malaise, and dyspnoea.
	Frequency unknown	Hypersensitivity syndrome, which may include in addition to the above dermatomyositis, purpura, leukopenia, haemolytic anaemia, positive ANA, asthenia, chills, toxic epidermal necrolysis, erythema multiforme, Stevens-

MedDRA system organ class	**Frequency**	**Adverse reactions**
		Johnson syndrome.
Endocrine disorders	Frequent	Diabetes mellitus
Metabolism and nutrition disorders	Frequency unknown	Weight gain
Psychiatric disorders	Frequency unknown	Depression
Nervous system disorders	Frequent	Headache, insomnia
	Less frequent	Dizziness, fatigue, asthenia, paraesthesia, peripheral neuropathy.
	Frequency unknown	Cognitive impairment (memory loss, forgetfulness, amnesia, memory impairment, confusion).
Ear and labyrinth disorders	Frequent	Vertigo.
Cardiac disorders	Frequent	Atrial fibrillation.
Respiratory, thoracic and mediastinal disorders	Frequent	Bronchitis, sinusitis.
	Frequency unknown	Interstitial lung disease.
Gastrointestinal disorders	Frequent	Constipation, diarrhoea, nausea, vomiting, flatulence, dyspepsia,

MedDRA system organ class	**Frequency**	**Adverse reactions**
		abdominal pain, cramps, [and] pancreatitis, gastritis.
Hepato-biliary disorders	Frequency unknown	Hepatitis, jaundice, fatal and non-fatal hepatic failure.
Skin and subcutaneous tissue disorders	Frequent	Skin rash, alopecia, eczema.
	Frequency unknown	Pruritus, skin changes (nodules, discolouration, dryness of skin/mucous membranes, changes to hair or nails) (see **"Immune system disorders"**).
Musculoskeletal and connective tissue disorders	Frequent	Myalgia, muscle cramps.
	Less frequent	Myopathy, myositis, rhabdomyolysis presenting as muscle pain with elevated creatine phosphokinase and myoglobinuria leading to renal failure, arthralgia (see **"Immune system disorders"**).
Reproductive system and breast disorders	Frequency unknown	Erectile dysfunction
General disorders	Frequent	Oedema/swelling.
Investigations	Frequent	Marked and persistent increases

MedDRA system organ class	Frequency	Adverse reactions
		of serum transaminases and elevated alkaline phosphatase and gamma-glutamyl transpeptidase, liver function test abnormalities (mild and transient), increases in serum creatinine kinase (CK) levels derived from skeletal muscle (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

The applicant can be reached at the following contact number: 010 045 2500.

4.9 Overdose

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: A 7.5 Serum-cholesterol reducers.

Pharmacotherapeutic group: HMG CoA reductase inhibitors. ATC code: C10AA01

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

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 hydroxy anisole

Citric acid monohydrate

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Pregelatinized starch

Film-coating:

Opadry Pink 20A54535

Coating material contains:

Hydroxypropyl cellulose

Hypromellose

Iron oxide red

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 °C

Protect from light.

Keep the blisters in the outer carton until required for use.

6.5 Nature and contents of container

Blister pack comprises of non-toxic, white opaque, PVC/PVDC film with backing of plain blister foil with VMCH coating.

Suitable number of blister strips will be placed in an outer cardboard carton.

Blister strips of 10's is packed into unit cartons for pack sizes of 30's.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Strides Pharma SA (Pty) Ltd.

106 16th Road

Building 2

Midrand

1685

8 REGISTRATION NUMBER(S)

ROLTESIM 40: A38/7.5/0372

ROLTESIM 80: A38/7.5/0373

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 February 2005

10 DATE OF REVISION OF THE TEXT

24 November 2022