SCHEDULING STATUS: S4

PROPRIETARY NAME (AND DOSAGE FORM):
ROLTESIM 40 (Tablets)
ROLTESIM 80 (Tablets)

COMPOSITION:
ROLTESIM 40: Each film-coated tablet contains 40 mg ROLTESIM. Inactive ingredients include ascorbic acid, butylated hydroxyl-anisole, citric acid monohydrate, hydroxypropyl cellulose, hypromellose, iron oxide red, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinised starch, talc, and titanium dioxide.
ROLTESIM 80: Each film-coated tablet contains 80 mg ROLTESIM. Inactive ingredients include ascorbic acid, butylated hydroxyl-anisole, citric acid monohydrate, hydroxypropyl cellulose, hypromellose, iron oxide red, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinised starch, talc, and titanium dioxide.
Contains lactose.

PHARMACOLOGICAL CLASSIFICATION:
A 7.5 Serum-cholesterol reducers.

PHARMACOLOGICAL ACTION:
Pharmacodynamics:
ROLTESIM is a cholesterol-lowering agent derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion ROLTESIM, 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, ROLTESIM, reduces total plasma cholesterol, low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) cholesterol concentrations. Apolipoprotein B is also decreased. In addition, ROLTESIM moderately increases high-density lipoprotein (HDL) cholesterol and variably reduces plasma triglycerides.

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

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.

CONTRAINDICATIONS:
- Hypersensitivity to ROLTESIM, 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 **"WARNINGS"** and **"PREGNANCY AND LACTATION"**).
- 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 **"INTERACTIONS"** and **"Special Precautions"**).
- Concomitant administration of gemfibrozil, ciclosporin or danazol (see **"INTERACTIONS"** and **"Special Precautions"**).

WARNINGS:
The active metabolite of **ROLTESIM** is fetotoxic and teratogenic in rats, and it should therefore not be used in female patients of child-bearing potential (see **"CONTRAINDICATIONS"** and **"PREGNANCY AND LACTATION"**).

Use in paediatric patients is not recommended, as safety and efficacy have not been established.
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 ROLTESIM. Therefore, the 80 mg dose of ROLTESIM should be used only in patients who have been taking ROLTESIM 80 mg chronically (e.g. for 12 months or more) without evidence of muscle toxicity (see "DOSAGE AND DIRECTIONS FOR USE"). If, however, a patient who is currently tolerating the 80 mg dose of ROLTESIM needs to be initiated on an interacting medicine that is contraindicated (see "CONTRAINDICATIONS") or is associated with a dose cap for ROLTESIM, 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 (see **"Special Precautions"**).

Many of the patients who have developed rhabdomyolysis on therapy with ROLTESIM, 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 (see **"Special Precautions"**).

Persistent increases (to more than 3 x the Upper Limit of Normal – ULN) in serum transaminases have occurred in patients who received ROLTESIM, 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 ROLTESIM, 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** .

INTERACTIONS:
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 contraindicated (see **"CONTRAINDICATIONS"**). 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 (see **"WARNINGS"**).
In vitro studies have demonstrated a potential for voriconazole to inhibit the metabolism of ROLTESIM. 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 contraindicated (see **"CONTRAINDICATIONS"**).

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, HIV protease inhibitors, Nefazodone. Gemfibrozil, Ciclosporin, Danazol.	Contraindicated with **ROLTESIM** .
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 ROLTESIM, 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** .

PREGNANCY AND LACTATION:
Safety in pregnancy and lactation has not been established. The active metabolite of **ROLTESIM** is fetotoxic and teratogenic in rats, and it should therefore not be used in female patients of child-bearing potential (see **"CONTRAINDICATIONS"** and **"WARNINGS"**).

DOSAGE AND DIRECTIONS FOR USE:
The patient must follow a cholesterol-lowering diet before initiation of, and while on **ROLTESIM** therapy. The tablet should be swallowed whole.
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 80 mg daily as a single dose in the evening (see **"WARNINGS"**).
ROLTESIM can be taken with meals or on an empty stomach.
Dosage in 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 **"INTERACTIONS"**). A maximum daily dose of 10 mg **ROLTESIM** is recommended in patients taking ciclosporin, fibrates or niacin concomitantly (see **"INTERACTIONS"**).

SIDE EFFECTS AND SPECIAL PRECAUTIONS:
Side effects:

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-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, abdominal pain, cramps, and pancreatitis, gastritis.
Hepatobiliary 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, connective tissue and bone 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 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 **"Special Precautions"**).

Special Precautions:
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 (see **"WARNINGS"**). 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) (see **"WARNINGS"**).

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 (see **"WARNINGS"**).
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 contraindicated (see **"CONTRAINDICATIONS"** and **"INTERACTIONS"**).

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** .

Effects on the ability to drive and operate machinery:
ROLTESIM may cause dizziness or vertigo. Therefore, patients should be advised not to drive or operate machinery until individual susceptibility is known.

KNOWN SYMPTOMS OF OVER-DOSAGE AND PARTICULARS OF ITS TREATMENT:
(See **"SIDE EFFECTS AND SPECIAL PRECAUTIONS"**.)
General measures should be adopted and liver function should be monitored. Treatment is symptomatic and supportive.

IDENTIFICATION:
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.

PRESENTATION:
White opqaue PVC/PVDC and Aluminium foil blister strips of 10 tablets, packed in 30's.

STORAGE INSTRUCTIONS:
Store in a dry place at or below 25 ºC. Protect from light. Keep the blisters in the outer carton until required for use. **KEEP OUT OF REACH OF CHILDREN.**

REGISTRATION NUMBERS:
ROLTESIM 40: A38/7.5/0372
ROLTESIM 80: A38/7.5/0373

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION:
STRIDES PHARMA (SA) (Pty) LTD. 106 16th Road, Midrand, 1686, South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT:
20 July 2012

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SKEDULERINGSTATUS: S4

EIENDOMSNAAM (EN DOSEERVORM):
ROLTESIM 40 (Tablette)
ROLTESIM 80 (Tablette)

SAMESTELLING:
ROLTESIM 40: Elke film-bedekte tablet bevat 40 mg simvastatien. Onaktiewe bestanddele sluit in, askorbiensuur, gebutileerde hidroksi-anisool, sitroensuurmonohidraat, hidroksiepropielsellulose, hipromellose, rooi ysteroksied, laktosemonohidraat, magnesiumstearaat, mikrokristallien sellulose, gepregelatiniseerde stysel, talk en titanium dioksied.
ROLTESIM 80: Elke film-bedekte tablet bevat 80 mg simvastatien. Onaktiewe bestanddele sluit in, askorbiensuur, gebutileerde hidroksi-anisool, sitroensuurmonohidraat, hidroksiepropielsellulose, hipromellose, rooi ysteroksied, laktosemonohidraat, magnesiumstearaat, mikrokristallien sellulose, gepregelatiniseerde stysel, talk en titanium dioksied.
Bevat laktose.

FARMAKOLOGIESE KLASSIFISERING:
A 7.5 Serumcholesterolreduseerders.

FARMAKOLOGIESE WERKING:
Farmakodinamika:
Simvastatien is 'n cholesterol-verlagende middel wat sinteties van 'n fermentasie produk van *Aspergillus terreus* afgelei word. Na orale inname word simvastatien, 'n onaktiewe laktoon, gehidroliseer na die ooreenstemmende beta-hidroksisuur, wat die aktiewe vorm verteenwoordig. Dit is 'n hoofmetaboliet en 'n inhibeerder van 3-hidroksi-3-metielglutariel-koënsiem A (HMG-KoA) reduktase, die ensiem wat die omsetting van HMG-KoA na mevalonaat kataliseer, 'n vroeë en tempo-beperkende stap in die biosintese van cholesterol. Gevolglik verminder simvastatien totale plasmacholesterol-, lae-densiteit- lipoproteïen (LDL)- en baie-lae-densiteit-lipoproteïen (VLDL)-cholesterolkonsentrasies. Apolipoproteïen B is ook verlaag. Daarbenewens verhoog simvastatien hoë-densiteit-lipoproteïen(HDL)-cholesterol matig en veroorsaak wisselende verlagings van plasmatrigliseriede.

Farmakokinetika:
Ekstensiewe pre-sistemiese ekstraksie deur die lewe vind plaas, en die orale biobeskikbaarheid van die aktiewe medisyne of metaboliete is minder as 5 %. Meer as 95 % van simvastatien en sy beta-hidroksi-metaboliet is aan plasmaproteïene gebonde. Na 'n orale dosis, word piek plasmakonsentrasies van simvastatien binne 1 tot 2 uur waargeneem. Simvastatien word primêr deur die lewer uitgeskei, en minder as 13 % van sy metaboliete word in die urine uitgeskei.

INDIKASIES:
Hipercholesterolemie: ROLTESIM is aangedui in kombinasie met dieet, om verhoogde totale serumcholesterol en LDL-cholesterol te verlaag in pasiënte met:
- Primêre hipercholesterolemie;
- Heterosigotiese familiale hipercholesterolemie; of
- Gemengde hiperlipemie,

Wanneer die reaksie op dieet of ander nie-farmakologiese maatreëls alleen nie voldoende is nie.

Koronêre hartsiekte:
ROLTESIM is aangedui in pasiënte met koronêre hartsiekte en hipercholesterolemie wat nie op dieet reageer nie, om:
- Die risiko van totale mortaliteit te verlaag, deur koronêre sterftes te verminder,
- Die risiko van nie-fatale miokardiale infarksie te verminder,
- Die risiko te verlaag dat 'n persoon miokardiale hervaskulariseringsprosedures (koronêre arterie omleiding-hegting en perkutane transluminale koronêre angioplastie) moet ondergaan, en
- Die progressie van koronêre aterosklerose te vertraag.

KONTRAÏNDIKASIES:
- Hipersensitiwiteit teenoor simvastatien, ander HMG-KoA-reduktase-inhibeerders, of enige van die bestanddele in **ROLTESIM** .
- Akute of chroniese lewersiekte.
- Onverklaarbare aanhoudende verhogings van serumtransaminases.
- Swangerskap en laktasie (sien **"WAARSKUWINGS"** en **"SWANGESKAP EN LAKTASIE"**).
- Porfirie: Veiligheid is nie vasgestel nie.
- Gelyke toediening van kragtige CYP3A4 inhibeerders, bv. itrakonasool, ketakonasool, posakonasool, MIV protease inhibeerders, eritromisien, klaritromisien, telitromisien en nefasodoon (sien **"INTERAKSIES"** en **"Spesiale Voorsorgmaatreëls"**).
- Gelyke toediening van gemfibrosil, siklosporien of danasol (sien **"INTERAKSIES"** en **"Spesiale Voorsorgmaatreëls"**).

WAARSKUWINGS:
Die aktiewe metaboliet van **ROLTESIM** is fetotoksies en teratogenies in rotte, en dit behoort dus nie in vroulike pasiënte met barende potensiaal gebruik te word nie (sien **"KONTRAÏNDIKASIES"** en **"SWANGESKAP EN LAKTASIE"**).

Gebruik in pediatriese pasiënte word nie aanbeveel, omdat veiligheid en doeltreffendheid nie vasgestel is nie.
ROLTESIM veroorsaak minder as gereeld dat miopatie gemanifesteer word as spierpyn, teerheid of swakheid met kreatienkinase (KK) bo tien keer die boonste limiet van normaal. Miopatie neem soms die vorm van rabdomioliese aan, met of sonder akute renale versaking sekondêr tot mioglobinurie, en sterftes het voorgekom. Die risiko van miopatie word verhoog deur hoë vlakke van statienaktiwiteit in plasma. Predisponerende faktore vir miopatie sluit in gevorderde ouderdom (≥ 65 jaar), vroulike geslag, onbeheerde hipotiroïdisme en renale inkorting.

Die risiko van miopatie, insluitend rabdomioliese, is dosisverwant. Die risiko van miopatie, insluitend rabdomioliese, is groter by pasiënte op ROLTESIM 80, in vergelyking met ander statienterapieë met soortgelyke of groter LDL-C-verlagende effektiwiteit en vergelyk met laer dosisse simvastatien. Dus, moet die 80 mg dosis van ROLTESIM slegs gebruik word by pasiënte wat 80 mg simvastatien chronies geneem het (bv. vir 12 maande of langer) sonder bewyse van spiertoksisiteit (sien "DOSERING EN GEBRUIKSAANWYSINGS"). Indien 'n pasiënt wat tans die 80 mg dosis ROLTESIM verdra, egter geïnisieer moet word op 'n interaktiewe medisyne wat gekontraïndikeerd is (sien " KONTRAÏNDIKASIES ") of geassosieerd is met 'n dosis perk vir simvastatien, moet daardie pasiënt oorgeskakel word na 'n alternatiewe statien met minder potensiaal vir hierdie medisyne-interaksie. Pasiënte moet in kennis gestel word van die verhoogde risiko van miopatie, insluitend rabdomioliese, en om onmiddellik onverklaarbare spierpyn, teerheid of swakheid aan te meld. Indien simptome voorkom, moet die behandeling onmiddellik gestaak word.

Alle pasiënte wat behandeling met ROLTESIM begin, of wie se dosis ROLTESIM verhoog word, moet in kennis gestel word van die risiko van miopatie, insluitend rabdomioliese, en hulle moet aangesê word om onmiddellik onverklaarbare spierpyn, teerheid of swakheid aan te meld. ROLTESIM terapie moet onmiddellik gestaak word indien miopatie gediagnoseer of vermoed word. In meeste gevalle klaar spiersimptome en verhoogde kreatienkinase (KK) op wanneer behandeling onmiddellik gestaak word. Periodieke KK-bepalings kan oorweeg word by pasiënte wat behandeling met **ROLTESIM** begin of wie se dosis verhoog word, maar daar is geen versekering dat sodanige monitering miopatie sal voorkom nie (sien "**Spesiale voorsorgmaatreëls**").

Baie van die pasiënte wat rabdomioliese ontwikkel het tydens behandeling met simvastatien, soos in **ROLTESIM** , het ingewikkelde mediese geskiedenis gehad, insluitend renale inkorting, gewoonlik as gevolg van langdurige diabetes mellitus. Sulke pasiënte vereis nouer monitering. **ROLTESIM** terapie moet gestaak word indien daar aansienlike verhoogde KK-vlakke voorkom of miopatie gediagnoseer of vermoed word. **ROLTESIM** terapie moet ook tydelik weerhou word by enige pasiënte wat 'n akute of ernstige toestand ondervind wat predisponerend is vir die ontwikkeling van renale versaking sekondêr tot rabdomioliese, bv. sepsis, hipotensie, groot operasies, trauma, ernstige metaboliese-, endokriene- of elektrolietafwykings, of onbeheerde epilepsie (sien "**Spesiale Voorsorgmaatreëls**").

Aanhoudende verhogings (tot meer as 3 x die Boonste Limiet van Normaal - BLN) in serumtransaminases het voorgekom by pasiënte wat simvastatien ontvang het, soos in ROLTESIM . Toe die behandeling gestaak of onderbreek was by hierdie pasiënte, het die transaminasevlakke gewoonlik stadig gedaal tot voorbehandelingsvlakke. Die verhogings hou nie verband met geelsug of ander kliniese tekens of simptome nie. Daar was geen bewyse van hipersensitiwiteit nie.
Daar word aanbeveel dat lewerfunksietoetse uitgevoer word voor die aanvang van die behandeling, en daarna indien klinies aangedui. Daar is na-bemarkingsverslae van fatale en nie-fatale hepatiese versaking by pasiënte wat statiene neem, insluitend **ROLTESIM .** Indien ernstige lewerskade met kliniese simptome en/of hiperbilirubinemie of geelsug voorkom tydens behandeling met **ROLTESIM** , moet die behandeling onmiddellik onderbreek word. Indien daar nie 'n alternatiewe etiologie gevind word nie, moet **ROLTESIM** nie hervat word nie. Let daarop dat alanienaminotransferase (ALT) uit spiere kan emaneer, daarom kan ALT verhogings tesame met KK miopatie aandui.

Matige (< 3 x BLN) verhogings van serumtransaminases is na behandeling met **ROLTESIM** aangemeld. Hierdie veranderinge het verskyn kort na die aanvang van die behandeling met simvastatien, insluitend **ROLTESIM** , was dikwels kortstondig, het geen simptome vergesel nie en het nie onderbreking van die behandeling vereis nie.

Verhogings in HbA1c en vastende serumglukosevlakke is by HMG-KoA reduktase inhibeerders, insluitend **ROLTESIM** , gerapporteer.

INTERAKSIES:
Miopatie veroorsaak deur interaksies van medisyne:
Gelyke toediening van medisyne wat sitochroom P450 isoënsiem CYP3A4 inhibeer, mag hoë plasmavlakke van **ROLTESIM** veroorsaak, wat dus die risiko van miopatie kan verhoog en is gekontraïndikeerd (sien **"KONTRAÏNDIKASIES"**). Medisyne wat sitochroom P450 isoënsiem CYP3A4 inhibeer, sluit in: siklosporien, itrakonasool, ketokonasool, eritromisien, klaritromisien, MIV-protease-inhibeerders, nefasodoon of groot hoeveelhede pomelosap (> 1 ℓ daagliks). Indien behandeling met itrakonasool, ketokonasool, posakonasool, eritromisien, klaritromisien, of telitromisien onvermydelik is, moet behandeling met **ROLTESIM** gestaak word tydens die duur van behandeling (sien **"WAARSKUWINGS"**).
In vitro studies het 'n potensiaal vir vorikonasool getoon om die metabolisme van simvastatien te inhibeer. Aanpassing van die **ROLTESIM** dosis mag nodig wees om die risiko van miopatie, insluitend rabdomioliese, te verminder, indien vorikonasool saam met **ROLTESIM** moet gebruik word

Die gesamentlike gebruik van **ROLTESIM** met gemfibrosil, siklosporien, of danasol is gekontraïndikeerd (sien **"KONTRAÏNDIKASIES"**).

Die risiko van miopatie word verhoog wanneer ander medisyne wat miopatie veroorsaak, soos fibrate en niasien, saam met **ROLTESIM** toegedien word. 'n Maksimum dosis van 10 mg **ROLTESIM** daagliks word aanbeveel by pasiënte wat ander fibrate of lipiedverlagende dosisse niasien neem (nikotiensuur). Die voordele van die gekombineerde gebruik van **ROLTESIM** met die volgende medisyne moet noukeurig opgeweeg word teen die moontlike risiko's van kombinasies: amiodaroon, verapamiel, diltiasiem of amilodopien (sien Tabel 1).

Tabel 1: Medisyne interaksies geassosieerd met verhoogde risiko van miopatie/rabdomioliese:

Interaktiewe medisyne	Voorskrif aanbevelings
Kragtige CYP3A4 inhibeerders, bv.: Itrakonasool, Ketokonasool, Posakonasool, Eritromisien, Klaritromisien Telitromisien, MIV-protease-inhibeerders, Nefasodoon Gemfibrosil, Siklosporien, Danasol	Gekontraïndikeerd met **ROLTESIM** .
Verapamiel, Diltiasiem	Moet nie 10 mg **ROLTESIM** daagliks oorskry nie.
Amiodaroon, Amlodipien	Moet nie 20 mg **ROLTESIM** daagliks oorskry nie.
Pomelosap	Vermy groot hoeveelhede pomelosap (> 1 ℓ daagliks).

Kolgisien
Gevalle van miopatie, insluitend rabdomioliese, is aangemeld met simvastatien, soos in **ROLTESIM** , wat gesamentlik met kolgisien toegedien is, en sorg word aanbeveel wanneer **ROLTESIM** met kolgisien voorgeskryf word.
Digoksien:
ROLTESIM mag verhogings in digoksienvlakke veroorsaak.
Kumarienderivate (bv. warfarien):
'n Moontlike toename in die antikoagulasie uitwerking van die kumarienantikoagulante mag voorkom. Pasiënte wat 'n kumarienantikoagulant neem, behoort hulle IGV te laat bepaal voordat hulle met **ROLTESIM** terapie begin. Die IGV moet dikwels genoeg gemoniteer word in die vroeë stadiums van terapie totdat dit stabiliseer. Wanneer 'n stabiele IGV aangeteken is, kan die IGV gemoniteer word met tussenposes wat gewoonlik vir pasiënte op kumarien-antikoagulante aanbeveel word. Wanneer 'n dosisaanpassing van **ROLTESIM** plaasvind, moet hierdie prosedure herhaal word.
Galsuursekwestrante:
ROLTESIM behoort 1 uur voor, of 4 uur na cholestiramien geneem te word. Gelyktydige gebruik mag die biobeskikbaarheid van **ROLTESIM** verlaag.

SWANGERSKAP EN LAKTASIE:
Veiligheid in swangerskap en laktasie is nie vasgestel nie.
Die aktiewe metaboliet van **ROLTESIM** is fetotoksies en teratogenies in rotte, en dit behoort dus nie in vroulike pasiënte met barende potensiaal gebruik te word nie (sien **"KONTRAÏNDIKASIES"** en **"WAARSKUWINGS"**).

DOSERING EN GEBRUIKSAANWYSINGS:
Die pasiënt moet 'n cholesterol-verlagende dieet voor instelling van, en tydens **ROLTESIM** terapie volg. Die tablet moet heel ingesluk word.
Hipercholesterolemie:
Volwassenes: Aanvangsdosis: 10 mg daagliks as 'n enkele dosis in die aand. Die dosis **ROLTESIM** moet verminder word as LDL-cholesterolvlakke onder 1,94 mmol/ℓ, daal, of as totale plasmacholesterolvlakke tot onder 3,6 mmol/ℓ, daal.
Koronêre hartsiekte:
Volwassenes: Aanvangsdosis: 20 mg/dag as 'n enkele dosis in die aand.
Dosisaanpassings:
Indien nodig behoort die dosis met tussenposes van nie minder as 4 weke aangepas te word, tot 'n maksimum van 80 mg daagliks as 'n enkele dosis in die aand (see **"WAARSKUWINGS"**). **ROLTESIM** kan saam met maaltye of op 'n leë maag geneem word.
Dosering in renale ontoereikendheid:
ROLTESIM ondergaan nie beduidende renale uitskeiding nie; dosisaanpassing behoort dus nie in pasiënte met ligte tot matige renale ontoereikendheid nodig te wees nie. In pasiënte met ernstige renale ontoereikendheid behoort **ROLTESIM** terapie noukeurige gemoniteer te word en dosisse bokant 10 mg/dag moet met omsigtigheid geïmplementeer word.
Gelyktydige terapie:
ROLTESIM is effektief alleen of in kombinasie met galsuursekwestrante. Wanneer beide medisyne voorgeskryf word, moet **ROLTESIM** 1 uur voor of 4 ure na cholestiramien toegedien word (sien "**INTERAKSIES**"). 'n Maksimum daaglikse dosis van 10 mg **ROLTESIM** word aanbeveel by pasiënte wat siklosporien, fibrate of nasien gelyktydig neem (sien "**INTERAKSIES**").

NEWE-EFFEKTE EN SPESIALE VOORSORGMAATREËLS:
Newe-effekte:

Infeksies en infestasies:
Gereeld: Boonste lugweginfeksie, urienweginfeksie.
Bloed- en die limfstelselversteurings:
Gereeld: Anemie, neutropenie (see **"Immuunstelsel versteurings"**).
Immuunstelsel versteurings:
Minder gereeld: Reaksies kan angioedeem, lupusagtige sindroom, polimialgie-rumatiek, vaskulitis, trombositopenie, verhoogde eritrosiet sedimentasie tempo, eosinofilie, artritis, artralgie, urtikaria, fotosensitiwiteit, koors, blosing, malaise en dispnee insluit.
Frekwensie onbekend: Hipersensitiwiteitsindroom, wat benewens bogenoemde dermatomiositis, purpura, leukopenie, hemolitiese anemie, positiewe ANA, astenie, kouekoors, toksiese epidermale nekrolise, eriteem multiforme, Stevens-Johnson sindroom kan insluit.
Endokriene versteurings:
Gereeld: Diabetes mellitus.
Metabolisme- en voedingsversteurings:
Frekwensie onbekend: Gewigstoename.
Psigiatriese versteurings:
Frekwensie onbekend: Depressie.
Senusisteemversteurings:
Gereeld: Hoofpyn, slapeloosheid.
Minder gereeld: Duiseligheid, moegheid, astenie, parestesie, perifere neuropatie.
Frekwensie onbekend: Kognitiewe gebrek (geheueverlies, vergeetagtigheid, amnesie, geheue gebrek, verwardheid).
Oor- en doolhofversteurings:
Gereeld: Vertigo.
Kardiale versteurings:
Gereeld: Atriale fibrillasie.
Respiratories-, torakale- en mediastinale versteurings:
Gereeld: Brongitis, sinusitis.
Frekwensie onbekend: Interstisiële longsiekte.
Gastroïntestinale versteurings:
Gereeld: Hardlywigheid, diarree, naarheid, braking, winderigheid, dispepsie, abdominale pyn, krampe en pankreatitis, gastritis.
Hepato-biliêre versteurings:
Frekwensie onbekend: Hepatitis, geelsug, fatale en nie-fatale hepatiese versaking.
Vel- en onderhuidse weefselversteurings:
Gereeld: Veluitslag, alopesie, ekseem.
Frekwensie onbekend: Pruritus, vel veranderinge (nodules, verkleuring, droogheid van vel/mukusmembrane, veranderinge in hare of naels) (sien **"Immuunstelsel versteurings"**).
Muskuloskeletale-, bindweefsel- en been versteurings:
Gereeld: Mialgie, spierkrampe.
Minder gereeld: Miopatie, miositis, rabdomioliese wat presenteer as spierpyn met verhoogde kreatienfosfokinase en mioglobinurie wat lei tot renale versaking, artralgie (sien **"Immuunstelsel versteurings"**).
Voortplantingstelsel- en borsafwykings:
Frekwensie onbekend: Erektiele disfunksie.
Algemene versteurings:
Gereeld: Edeem/swelling.
Ondersoeke:
Gereeld: Uitgesproke en aanhoudende verhogings in serumtransaminases en verhoogde alkaliese fosfatase en gamma-glutamiel-transpeptidase, lewerfunksietoets-abnormaliteite (lig en verbygaande), verhogings in serum kreatinienkinase (KK) vlakke wat van skeletspier ontstaan (sien **"Spesiale voorsorgmaatreëls"**).

Spesiale Voorsorgmaatreëls:
ROLTESIM moet met omsigtigheid gebruik word in pasiënte wie:
- Aansienlike hoeveelhede alkohol inneem en/of 'n geskiedenis van lewersiekte het.
- Geneig mag wees om renale versaking sekondêr tot rabdomioliese te ontwikkel, soos dié met ernstige, akute infeksie, hipotensie, ernstige metaboliese, endokriene of elektrolietversteurings, onbeheerde konvulsies, groot operasies of trouma (sien **"WAARSKUWINGS"**). Daar bestaan 'n verhoogde risiko van ontwikkeling van renale versaking indien rabdomioliese voorkom.
- Ernstige renale inkorting het.

Hepatiese effekte:
Lewerfunksietoetse, insluitend bepalings van serumtransaminase word aanbeveel voor instelling van **ROLTESIM** terapie en periodiek tot een jaar na die laaste dosisverhoging. **ROLTESIM** moet gestaak word indien die verhoging in transaminasevlakke aanhou en/of toeneem tot drie keer of meer van die boonste limiet van normaal (BLN) (sien **"WAARSKUWINGS"**).

Miopatie:
Verlaging van die risiko van miopatie:
1. Algemene maatreëls
   Pasiënte wat terapie met **ROLTESIM** begin, moet ingelig word oor die risiko van miopatie en behoort onmiddellik onverklaarbare spierpyn, -teerheid of -swakheid aan te meld. 'n Kreatienkinase (KK) vlak bokant 10 keer die Boonste Limiet van Normaal (BLN) in 'n pasiënt, met onverklaarbare simptome, dui op miopatie. **ROLTESIM** behoort gestaak te word indien miopatie gediagnoseer of vermoed word (sien **"WAARSKUWINGS"**).
2. Maatreëls om die risiko van miopatie wat deur interaksies met medisyne veroorsaak word, te verminder
   Die voordele en risiko's van die gelyktydige gebruik van **ROLTESIM** saam met immuunonderdrukkende middels, fibrate of lipied-verlagende dosisse niasien moet versigtig oorweeg word, en die dosis **ROLTESIM** behoort gewoonlik nie 10 mg/dag te oorskry nie. Gelyktydige toediening met siklosporien, itrakonasool, ketokonasool, eritromisien, klaritromisien, MIV-protease-inhibeerders, en nefasodoon, is gekontraïndikeerd (sien **"KONTRAÏNDIKASIES"**).

Laktose:
ROLTESIM tablette bevat laktose. Pasiënte met seldsame oorerflike probleme van galaktose-onverdraagsaamheid, die Lapp-laktase-tekort of glukose-galaktose wanabsorpsie, moet nie **ROLTESIM** neem nie.

Uitwerking op die vermoë om te bestuur en masjinerie te gebruik:
ROLTESIM kan duiseligheid of vertigo veroorsaak. Daarom moet pasiënte aangeraai word om nie te bestuur of masjinerie te hanteer voordat individuele vatbaarheid bekend is nie.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN:
(See **"NEWE-EFFEKTE EN SPESIALE VOORSORGMAATREËLS"**.)
Algemene maatreëls moet gebruik, en lewerfunksie moet gemoniteer word. Behandeling is simptomaties en ondersteunend.

IDENTIFICATION:
ROLTESIM 40:
Pienk-kleurige, ovaal, bikonvekse, ongeskonde, film-bedekte tablette ontbossing met 'SVN 40' aan die een kant en plein aan die ander kant.
ROLTESIM 80:
Pienk-kleurige, kapsulevormige, bikonvekse, ongeskonde, film-bedekte tablette ontbossing met 'SVN 80' aan die een kant en 'n keep op die ander kant.

AANBIEDING:
Wit opaak PVC/PVDC en aluminium foelie stolpverpakking strokies van 10 tablette, verpak in 30's.

BERGINGSAANWYSINGS:
Berg in 'n droë plek teen of benede 25 ºC. Beskerm teen lig. Hou die stolpverpakkings in die buitenste karton totdat dit benodig word vir gebruik. **HOU BUITE BEREIK VAN KINDERS.**

REGISTRASIENOMMERS:
ROLTESIM 40: A38/7.5/0372
ROLTESIM 80: A38/7.5/0373

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