PROFESSIONAL INFORMATION FOR ROSUTERO

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

ROSUTERO 5 mg (film-coated tablet)

ROSUTERO 10 mg (film-coated tablet)

ROSUTERO 20 mg (film-coated tablet)

ROSUTERO 40 mg (film-coated tablet)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ROSUTERO 5 mg

Each film-coated tablet contains 5 mg of Rosuvastatin (as Rosuvastatin Calcium).

ROSUTERO 10 mg

Each film-coated tablet contains 10 mg of Rosuvastatin (as Rosuvastatin Calcium)

ROSUTERO 20 mg

Each film-coated tablet contains 20 mg of Rosuvastatin (as Rosuvastatin Calcium)

ROSUTERO 40 mg

Each film-coated tablet contains 40 mg of Rosuvastatin (as Rosuvastatin Calcium)

Contains sugar: lactose monohydrate.

ROSUTERO 5 mg: contains 31,300 mg lactose monohydrate.

ROSUTERO 10 mg: contains 62,600 mg lactose monohydrate.

ROSUTERO 20 mg: contains 125,200 mg lactose monohydrate.

ROSUTERO 40 mg: contains 250,400 mg lactose monohydrate.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

ROSUTERO 5 mg

Light yellow to yellow, round, bevel-edged biconvex film-coated tablets debossed with 'H' on one side and 'R3' on the other side.

ROSUTERO 10 mg

Light pink to pink, round, bevel-edged biconvex film-coated tablets debossed with 'H' on one side and 'R4' on the other side.

ROSUTERO 20 mg

Light pink to pink, round, bevel-edged biconvex film-coated tablets debossed with 'H' on one, side and 'R5' on the other side.

ROSUTERO 40 mg

Light pink to pink, oval, bevel-edged biconvex film-coated tablets debossed with 'H' on one side and 'R6' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

To reduce the risk of cardiovascular events

In adult patients with an increased risk of atherosclerotic cardiovascular disease based on the presence of cardiovascular disease risk markers such as an elevated high-sensitivity C-reactive protein (hsCRP) level, age, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, ROSUTERO is indicated to reduce the risk of non- fatal stroke, non-fatal MI, and the need for arterial revascularisation.

In adult patients with hypercholesterolaemia

- ROSUTERO is indicated for patients with primary hypercholesterolaemia, mixed dyslipidaemia and isolated hypertriglyceridaemia (including Fredrickson Type IIa, IIb and IV; and heterozygous familial and non- familial hypercholesterolaemia) as an adjunct to diet when response to diet and exercise is inadequate.
- ROSUTERO is indicated to treat patients with primary dysbetalipoproteinaemia (FredricksonType III hyperlipoproteinaemia).
- ROSUTERO is also indicated to reduce Total Cholesterol and LDL-C in patients with homozygous familial hypercholesterolaemia, either alone or as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis).

ROSUTERO 40 mg should only be considered in patients with severe hypercholesterolaemia and high cardiovascular risk who do not achieve their treatment goal on 20 mg of ROSUTERO or alternative therapy.

Specialist supervision is recommended when the 40 mg dose is initiated (see section 4.4).

Children and adolescents 10-17 years of age

ROSUTERO is indicated to reduce the Total Cholesterol, LDL-C and Apo B in patients with heterozygous familial hypercholesterolaemia (HeFH).

4.2 Posology and method of administration

Before treatment initiation, the patient should be placed on a standard cholesterol-lowering diet that should continue during treatment.

Posology

Treatment of hypercholesterolaemia:

The recommended starting dose is 5 mg once a day.

The dose range for ROSUTERO is 5 - 40 mg once a day.

The dose should be individualised according to the goal of therapy and patient response. Most patients are controlled at the 10 mg dose. However, if necessary, dose adjustment can be made at 4 week intervals.

Adults:

Primary hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), mixed dyslipidaemia, dysbetalipoproteinaemia (Fredrickson Type III hyperlipoproteinaemia), and isolated hypertriglyceridaemia:

The recommended starting dose is 5 mg once a day.

For patients with severe hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), a start dose of 20 mg may be considered.

Homozygous familial hypercholesterolaemia:

For patients with homozygous familial hypercholesterolaemia a starting dose of 20 mg once a day is recommended.

Special Populations

Elderly:

The usual dose range applies.

Patients with renal insufficiency:

The recommended starting dose is 5 mg in patients with moderate renal impairment (creatinine clearance <60 ml/min). The 40 mg dose is contraindicated in patients with moderate renal impairment. All doses of ROSUTERO are contraindicated in patients with severe renal impairment (see sections 4.3 and 5.2).

Patients with hepatic insufficiency:

The usual starting dose of 5 mg applies in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment should start therapy with ROSUTERO 5 mg. Increased systemic exposure to rosuvastatin has been observed in these patients, therefore the use of doses above ROSUTERO 10 mg should be carefully considered (see section 5.2). ROSUTERO is contraindicated in patients with active liver disease (see section 4.3).

Race:

A 5 mg starting dose of ROSUTERO should be considered for Asian patients. Increased plasma concentration of rosuvastatin has been seen in Asian subjects (see section 4.4 and 5.2). The increased systemic exposure should be taken into consideration when treating Asian patients whose hypercholesterolaemia is not adequately controlled at doses up to 20 mg daily. The 40 mg dose is contraindicated in these patients.

Concomitant therapy:

Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when ROSUTERO is administered concomitantly with certain medicines that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g. ciclosporin and certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir, and/or tipranavir (see section 4.4 & 4.5).

It is recommended that prescribers consult the relevant product information when considering administration of such products together with ROSUTERO. Whenever possible, alternative medicines should be considered, and if necessary, consider temporarily discontinuing ROSUTERO therapy. In situations where co-administration of these medicinal products with ROSUTERO is unavoidable, the benefit and the risk of concurrent treatment and ROSUTERO dosing adjustments should be carefully considered (see section 4.4).

Paediatric population

Children and adolescents 10-17 years of age:

In children and adolescents with homozygous familial hypercholesterolaemia experience is limited to a small number of patients (aged 8 years and above).

In children and adolescents with heterozygous familial hypercholesterolaemia the usual dose range is 5-20 mg orally once daily. The dose should be appropriately titrated to achieve treatment goal. Safety and efficacy have not been established in this population of doses greater than 20 mg.

Method of administration

For oral use. ROSUTERO may be given at any time of the day, with or without food.

4.3 Contraindications

ROSUTERO is contraindicated in:

- hypersensitivity to rosuvastatin or to any of the excipients of ROSUTERO, listed in section 6.1.
- patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 times the upper limit of normal (ULN).
- patients with severe renal impairment (creatinine clearance <30 ml/min).
- patients with myopathy.
- concomitant use with ciclosporin (see section 4.5).
- pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.
- The 40 mg dose is contraindicated in patients with pre-disposing factors formyopathy/ rhabdomyolisis. Such factors include:
    - moderate renal impairment (creatinine clearance < 60 ml/min).
    - hypothyroidism.
    - personal or family history of hereditary muscular disorders.
    - previous history of muscular toxicity with another HMG-CoA reductase inhibitor or

fibrate.

- o alcohol abuse.
- o situations where an increase in plasma levels may occur.
- o Asian patients.
- o concomitant use of fibrates (see sections 4.4, 4.5 and 5.2).

4.4 Special warnings and precautions for use

The use of statin as in ROSUTERO has been associated with a risk of myasthenia gravis and ocular myasthenia.

Renal effects

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of rosuvastatin as in ROSUTERO, in particular 40 mg, where it was transient or intermittent in most cases. Proteinuria has not been shown to be predictive of acute or progressive renal disease (see section 4.8). Therefore, assessment of renal function should be considered during routine follow- up of patients treated with a dose of 40 mg.

Liver Effects

Liver enzyme tests should be performed in patients before initiating ROSUTERO therapy and as clinically indicated thereafter. If serious liver injury with clinical symptoms and/or hyperbilirubinaemia or jaundice occurs during treatment, therapy should be interrupted. If an alternate aetiology is not found, ROSUTERO should not be restarted.

ROSUTERO should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of chronic liver disease. Active liver disease, which may include unexplained persistent transaminase elevations, is a contra-indication to the use of ROSUTERO (see section 4.2)

It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation

of treatment. ROSUTERO must be discontinued, or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal. The reporting rate for serious hepatic events (consisting mainly of increased hepatic transaminases) in post-marketing use is higher at the 40 mg dose.

Skeletal muscle effects

Effects on skeletal muscle e.g. myalgia, myopathy and rhabdomyolysis have been reported in patients treated with rosuvastatin as in ROSUTERO. The reporting rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose. Patients who develop any signs or symptoms suggestive of myopathy should have their Creatine kinase (CK) levels measured. ROSUTERO therapy should be discontinued if myopathy is diagnosed or suspected.

Creatine Kinase Measurement

Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of a plausible alternative cause of CK increase which may confound interpretation of the result. If CK levels are significantly elevated at baseline (>5xULN) a confirmatory test should be carried out within 5 – 7 days. If the repeat test confirms a baseline CK >5xULN, treatment should not be started.

Before Treatment

ROSUTERO should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- renal impairment
- hypothyroidism
- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- alcohol abuse
- age >70 years
- situations where an increase in plasma levels may occur (see sections 4.2, 4.5 and 5.2)

- concomitant use of fibrates.

In such patients the risk of treatment should be considered in relation to possible benefit and clinical monitoring is recommended. If CK levels are significantly elevated at baseline (>5xULN) treatment should not be started.

During treatment

Patients should be asked to report inexplicable muscle pain, weakness or cramps immediately, particularly if associated with malaise or fever. CK levels should be measured in these patients. Therapy should be discontinued if CK levels are markedly elevated (>5xULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤5xULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing ROSUTERO or an alternative HMG-CoA reductase inhibitor at the lowest dose with close monitoring. Routine monitoring of CK levels in asymptomatic patients is not warranted.

There have been reports of an immune-mediated necrotising myopathy clinically characterised by persistent proximal muscle weakness and elevated serum creatine kinase during treatment or following discontinuation of statins, including ROSUTERO. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required.

An increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with ciclosporin, fibric acid derivatives, including gemfibrozil, nicotinic acid, azole antifungals and macrolide antibiotics.

Fusidic acid

ROSUTERO 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). Patients 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 coadministration of ROSUTERO and fusidic acid should only be considered on a case by case basis and under close medical supervision.

ROSUTERO should be prescribed with caution in patients with pre-disposing factors for myopathy, such as renal impairment, advanced age and hypothyroidism or situations where an increase in plasma levels may occur (see section 4.5 and section 5.2).

ROSUTERO should not be used in any patient with an acute serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders; or uncontrolled seizures).

Diabetes Mellitus

Increases in glycosylated haemoglobin (HbA1c) and serum glucose levels have been observed in patients treated with statin as in ROSUTERO and in some instances these increases may exceed the threshold for the diagnosis of diabetes mellitus. Therefore, patients at risk (fasting glucose 5.6 to 6.9 mmol/l, BMI >30 kg/m2, raised triglycerides, hypertension) should be clinically and biochemically monitored.

Protease inhibitors

ROSUTERO should be used with caution in patients taking various protease inhibitors in combination with ritonavir as pharmacokinetic studies have shown an increase in the AUC and Cmax of rosuvastatin (see section 4.2 and section 4.4).

Interstitial Lung Disease

Cases of interstitial lung disease have been reported with some statins, 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 as in ROSUTERO therapy should be discontinued.

Race

Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians (see section 4.2 and section 5.3).

Lactose:

ROSUTERO contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take ROSUTERO.

4.5 Interaction with other medicines and other forms of interaction

Effect of co-administered medicines on ROSUTERO

Transporter protein inhibitors

Rosuvastatin as in ROSUTERO, is a substrate for certain transporter proteins including the hepatic uptake transporter organic-anion-transporting polypeptide 1B1 (OATP1B1) and efflux transporter breast-cancer-resistance protein (BCRP). Concomitant administration of ROSUTERO with medicines that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy (see sections 4.2, 4.4 and 4.5 Table 1).

Ciclosporin

ROSUTERO is contraindicated in patients receiving ciclosporin (see section 4.3). Concomitant administration did not affect plasma concentrations of ciclosporin. However, after co-administration with ciclosporin, rosuvastatin steady plasma concentration state $AUC_{(0-t)}$ increased up to 7- fold over

that reported in healthy volunteers administered the same dose of rosuvastatin (see section 4.2)

Protease inhibitors

Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure (see Table 1). The concomitant use of ROSUTERO and some protease inhibitor combinations may be considered after careful consideration of ROSUTERO dose adjustments based on the expected increase in rosuvastatin exposure (see sections4.2, 4.4 and 4.5 Table 1).

Gemfibrozil and other lipid-lowering medicines

Concomitant use of ROSUTERO and gemfibrozil resulted in a 2-fold increase in rosuvastatin Cmax and AUC (see section 4.4).

Based interaction studies no pharmacokinetic relevant interaction with fenofibrate is expected, however a pharmacodynamic interaction may occur. Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (> or equal to 1 g/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMGCoA reductase inhibitors. The 40 mg dose is contraindicated with concomitant use of a fibrate (see sections 4.3 and 4.4). These patients should also start with the 5 mg dose.

Ezetimibe

Concomitant use of 10 mg ROSUTERO and 10 mg ezetimibe resulted in a 1.2-fold increase in AUC of rosuvastatin in hypercholesterolaemic subjects (Table 1). A pharmacodynamic interaction, in terms of adverse effects, between ROSUTERO and ezetimibe cannot be ruled out (see section 4.4).

Antacids

The simultaneous dosing of ROSUTERO with an antacid suspension containing aluminium and magnesium hydroxide resulted in a decrease in rosuvastatin plasma concentration of approximately 50 %. This effect was mitigated when the antacid was dosed 2 hours after ROSUTERO. The clinical

relevance of this interaction has not been studied.

Erythromycin

Concomitant use of ROSUTERO and erythromycin resulted in a 20 % decrease in AUC and a 30 % decrease in Cmax of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Cytochrome P450 enzymes

Results from *in vitro* and *in vivo* studies show that rosuvastatin is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes. In addition, rosuvastatin is a poor substrate for these isoenzymes. Therefore, interactions resulting from cytochrome P450- mediated metabolism are not expected. No clinically relevant interactions have been observed between rosuvastatin and either fluconazole (an inhibitor of CYP2C9 and CYP3A4) or ketoconazole (an inhibitor of CYP2A6 and CYP3A4).

Interactions requiring rosuvastatin dose adjustments (see below Table 1):

When it is necessary to co-administer ROSUTERO with other medicines known to increase exposure to rosuvastatin, doses of ROSUTERO should be adjusted. Start with a 5 mg once daily dose of ROSUTERO if the expected increase in exposure (AUC) is approximately 2-fold or higher.

The maximum daily dose of ROSUTERO should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of ROSUTERO taken without interacting medicines, for example a 20 mg dose of ROSUTERO with gemfibrozil (1.9-fold increase), and a 10 mg dose of ROSUTERO with combination ritonavir/atazanavir (3.1-fold increase).

If medicine is observed to increase rosuvastatin AUC less than 2-fold, the starting dose need not be decreased but caution should be taken if increasing the ROSUTERO dose above 20 mg.

Table 1: Effect of co-administered medicines on rosuvastatin exposure

2-fold or greater than 2-fold increase in AUC of rosuvastatin

Interacting medicine dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
Sofosbuvir/velpatasvir/voxilaprevir (400 mg-100 mg-100 mg) + Voxilaprevir (100 mg) once daily for 15 days	10 mg single dose	7,4 -fold ↑
Ciclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 10 days	7,1-fold ↑
Darolutamide 600 mg BID, 5 days	5 mg, single dose	5,2-fold ↑
Regorafenib 160 mg OD, 14 days	5 mg single dose	3,8 -fold ↑
Atazanavir 300 mg/ritonavir 100 mg OD, 8 days	10 mg, single dose	3,1-fold ↑
Simeprevir 150 mg OD, 7 days	10 mg, single dose	2,8-fold ↑
Velpatasvir 100 mg OD	10 mg single dose	2,7 -fold ↑
Ombitasvir 25 mg/ paritaprevir 150 mg/ ritonavir 100 mg/dasabuvir 400 mg BID	5 mg single dose	2,6-fold ↑
Grazoprevir 200 mg/ elbasvir 50 mg OD	10 mg single dose	2,3-fold ↑
Glecaprevir 400 mg/ pibrentasvir 120 mg OD for 7 days	5 mg once daily	2,2-fold ↑
Lopinavir 400 mg/ritonavir 100 mg BID, 17 days	20 mg OD, 7 days	2,1-fold ↑
Clopidogrel 300 mg loading, followed by 75 mg at 24 hours	20 mg, single dose	2-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1,9-fold ↑

Less than 2-fold increase in AUC of rosuvastatin		
Interacting medicine dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
Eltrombopag 75 mg OD, 5 days	10 mg, single dose	1,6-fold ↑
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg OD, 7 days	1,5-fold ↑
Tipranavir 500 mg/ritonavir 200 mg BID, 11 days	10 mg, single dose	1,4-fold ↑
Dronedarone 400 mg BID	Not available	1,4-fold ↑
Itraconazole 200 mg OD, 5 days	10 mg or 80 mg, single dose	**1,4-fold ↑
Ezetimibe 10 mg OD, 14 days	10 mg, OD, 14 days	**1,2-fold ↑

Decrease in AUC of rosuvastatin		
Interacting medicine dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
Erythromycin 500 mg QID, 7 days	80 mg, single dose	20 % ↓
Baicalin 50 mg TID, 14 days	20 mg, single dose	47 % ↓

*Data given as x-fold change represent a simple ratio between co-administration and rosuvastatin alone.
Data given as % change represent % difference relative to rosuvastatin alone.
Increase is indicated as "↑", decrease as "↓".
**Several interaction studies have been performed at different ROSUTERO dosages, the table shows the most significant ratio
AUC = area under curve; OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily.

Effect of ROSUTERO on co-administered medicines

Warfarin

The pharmacokinetics of warfarin are not significantly affected following co-administration with ROSUTERO. However, co-administration of ROSUTERO and warfarin may result in a rise in INR compared to warfarin alone. Therefore, monitoring of INR is recommended in patients taking warfarin both at initiation or cessation of therapy with ROSUTERO or following dose adjustment.

Niacin

The risk of skeletal muscle effects may be enhanced when ROSUTERO is used in combination with lipid-modifying doses of niacin; caution should be used when prescribing with ROSUTERO.

Consideration should be given both to the benefit of lipid lowering by the use of ROSUTERO in HIV-infected patients receiving protease inhibitors and the potential risks of this increased rosuvastatin plasma concentrations when initiating and up-titrating ROSUTERO doses in patients treated with protease inhibitors, as the combination may lead to an increased incidence of adverse events (see section 4.2 and 4.4).

The lowest dose of ROSUTERO that provides therapeutic benefit to the patient should be used and

close monitoring of adverse events is indicated (see section 4.2).

Other medicines

Digoxin

Based on data from specific interaction studies no clinically relevant interaction with digoxin is expected.

Fusidic Acid

Interaction studies with rosuvastatin and fusidic acid have not been conducted. The risk of myopathy, including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with systemic fusidic acid is necessary, ROSUTERO treatment should be discontinued throughout the duration of the fusidic acid treatment (see section 4.4).

Oral contraceptive/hormone replacement therapy (HRT)

Concomitant use of rosuvastatin and an oral contraceptive can result in an increase in ethinyl oestradiol and norgestrel AUC of 26 % and 34 % respectively. These increased plasma levels should be considered when selecting oral contraceptive doses. Although there are no pharmacokinetic data available in women taking concomitant HRT, a similar effect cannot be excluded.

4.6 Fertility, pregnancy and lactation

Woman of childbearing potential

Women of child-bearing potential should use appropriate contraceptive measures.

Pregnancy

ROSUTERO is contraindicated in pregnancy.

Breastfeeding

ROSUTERO is contraindicated in lactation.

4.7 Effects on ability to drive and use machines

ROSUTERO may cause dizziness, therefore patients taking ROSUTERO should not drive or use machines until their individual susceptibility to dizziness is known.

4.8 Undesirable effects

Tabulated list of adverse reactions

System organ class	**Frequency**	**Adverse event**
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia
Immune system disorders	Less frequent	Hypersensitivity reactions including angioedema
Endocrine disorders	Frequent	Diabetes Mellitus[1]
Psychiatric disorders	Frequency unknown	Depression
Nervous system disorders	Frequent	Headache, dizziness
	Less frequent	Cognitive impairment such as memory loss, forgetfulness, amnesia, memory impairment and confusion, polyneuropathy
	Frequency unknown	Peripheral neuropathy, sleep disturbances (including insomnia and nightmares), myasthenia gravis
Eye disorders	Frequency unknown	Ocular myasthenia
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Cough dyspnoea
Gastrointestinal disorders	Frequent	Constipation, nausea, abdominal pain
	Less frequent	Pancreatitis

Hepato-biliary disorders	Less frequent	Increased hepatic transaminases, jaundice, hepatitis
	Frequency unknown	Fatal and non-fatal hepatic failure
Skin and subcutaneous tissue disorders	Less frequent	Pruritus, rash, urticaria
	Frequency unknown	Stevens- Johnson syndrome
Musculoskeletal and connective tissue disorders	Frequent	Myalgia
	Less frequent	Myopathy (including myositis) Rhabdomyolysis, which may occasionally be associated with impairment of renal function, arthralgia, Lupus-like syndrome, muscle rupture, athralgia
	Frequency unknown	Tendon disorders, sometimes complicated by rupture Immune- mediated necrotising myopathy
Renal and urinary disorders	Less frequent	Haematuria
	Frequency unknown	Proteinuria
Reproductive system and breast disorders	Less frequent	Gynaecomastia
General disorders and administration site conditions	Frequent	Asthenia

[1] Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI >30 kg/m2, raised triglycerides, history of hypertension).

Description of selected adverse reactions

Skeletal muscle effects

Rhabdomyolysis, which may occasionally be associated with impairment of renal function, has been reported with ROSUTERO.

Renal effects

Proteinuria (see Laboratory effects below).

Laboratory effects

A dose-related increase in liver transaminases and Creatine kinase (CK) has been observed in patients taking ROSUTERO. Increases in HbA1c have also been observed in patients treated with ROSUTERO (see section 4.4). Abnormal urinalysis testing (dipstick-positive proteinuria with haematuria) has been seen in patients taking ROSUTERO. The protein detected was mostly tubular in origin. In most cases, proteinuria decreases or disappears spontaneously on continued therapy, and is not predictive of acute or progressive renal disease.

Other effects

In ROSUTERO treated patients, there was no impairment of adrenocortical function.

The reporting rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose.

Paediatric population

Children and adolescents 10-17 years of age

The safety profile of ROSUTERO is similar in children or adolescent patients and adults although CK elevations > 10 x ULN and muscle symptoms following exercise or increased physical activity, which resolved with continued treatment, were observed more frequently in clinical trials of children and adolescents. However, the same warnings and special precautions for use in adults also apply to children and adolescents (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 requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to the Holder of certificate of registration through the mail: pvg.cdma@heterogroups.com.

4.9 Overdose

There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Liver function and CK levels should be monitored. Haemodialysis is unlikely to be of benefit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.5 Serum-cholesterol reducers

Pharmacotherapeutic group: HMG-CoA reductase inhibitors, ATC code: C10A A07.

Mechanism of action

Rosuvastatin is a lipid lowering medicine that acts by selective and competitive inhibition of HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis, leading to reduced hepatic synthesis of cholesterol and VLDL.

This is followed by increased number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL.

Pharmacodynamic effects

Overall, rosuvastatin reduces elevated LDL cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, non-HDL-C, VLDL-C, VLDL-TG and increases ApoA-I.

Rosuvastatin also lowers LDL-C/HDL-C, total C/HDL-C, non-HDL-C/HDL and ApoB/ApoA-I ratio's.

A therapeutic response to rosuvastatin is evident within 1 week of commencing therapy and 90 % of maximum response is usually achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

5.2 Pharmacokinetic properties

Absorption

Maximum rosuvastatin plasma concentrations are achieved approximately 5 hours after oral administration. The absolute bioavailability is approximately 20 %.

Distribution

Rosuvastatin is taken up extensively by the liver which is the primary site of cholesterol synthesis and LDL- C clearance. The volume of distribution of rosuvastatin is approximately 134 L. Approximately 90 % of rosuvastatin is bound to plasma proteins, mostly albumin.

Biotransformation

Rosuvastatin undergoes limited metabolism in humans (approximately 10 %) mainly to the N-desmethyl form.

Elimination

Approximately 90 % of the rosuvastatin dose is excreted unchanged in the faeces (consisting of absorbed and non-absorbed active substance) and the remaining part is excreted in urine. Approximately 5 % is excreted unchanged in urine. The plasma elimination half-life is approximately 19 hours.

Linearity

Systemic exposure of rosuvastatin increases in proportion to dose. There are no changes in pharmacokinetic parameters following multiple daily doses.

Special populations

Age

The pharmacokinetics of rosuvastatin in children and adolescents with heterozygous familial hypercholesterolaemia was similar to or lower than that of adult patients with dyslipidaemia (see

"Paediatric population" below).

Race

Pharmacokinetic studies show a 1,26-2,31 fold elevation in geometric mean $AUC_{(0-t)}$ in Asian subjects compared with Caucasians.

Renal insufficiency

In a study in subjects with varying degrees of renal impairment, mild to moderate renal disease had little influence on plasma concentrations of rosuvastatin. However, subjects with severe impairment (CrCl < 30 ml/min) had a 3-fold increase in plasma concentration and a 9-fold increase in the N-desmethyl metabolite concentration compared to healthy volunteers. Steady-state plasma concentrations of rosuvastatin in subjects undergoing haemodialysis were approximately 50 % greater compared to healthy volunteers.

Hepatic insufficiency

In a study with subjects with varying degrees of hepatic impairment, there was no evidence of increased exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, two subjects with Child- Pugh scores of 8 and 9 showed an increase in systemic exposure of at least 2-fold compared to subjects with lower Child-Pugh scores. There is no experience in subjects with Child-Pugh scores above 9.

Paediatric population

Two pharmacokinetic studies with rosuvastatin (given as tablets) in paediatric patients with heterozygous familial hypercholesterolaemia 10 to 17 or 6 to 17 years of age demonstrated that exposure in paediatric patients appears comparable to or lower than that in adult patients. Rosuvastatin exposure was predictable with respect to dose and time over a 2-year period.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Cellulose, microcrystalline (PH 102)

Crospovidone

Hydroxypropyl cellulose

Sodium hydrogen carbonate

Talc

Magnesium stearate

Coating

Opadry II yellow

Opadry II Pink

Titanium dioxide

Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ^{o}C.

Store in the original package.

Protect from light / moisture.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

ROSUTERO 5 mg, 10 mg, 20 and 40 mg

10's – Alu-Alu blister pack

10 tablets packed in PVC aluminium blister pack.

ROSUTERO 5 mg, 10 mg, 20 and 40 mg

1000's LDPE Bag

Low density polyethylene bag, with plain triple laminated bag with silica gel canister 5 g.

6.6 Special precautions for disposal and other handling

None

7 HOLDER OF CERTIFICATE OF REGISTRATION

Hetero Drugs South Africa (Pty) Ltd

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Building No.2, First Floor,

74 Waterfall Drive,

Midrand, 2066

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8 REGISTRATION NUMBER(S)

ROSUTERO 5: 59/7.5/0673
ROSUTERO 10: 59/7.5/0674
ROSUTERO 20: 59/7.5/0675
ROSUTERO 40: 59/7.5/0676

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF AUTHORISATION

17 June 2026

10 DATE OF REVISION OF THE TEXT

TBA