pharmaniaga®

ROXATIN

Rosuvastatin

ROXATIN TABLET 10 MG
ROXATIN TABLET 20 MG

COMPOSITION

Roxatin Tablet 10 mg
Each film coated tablet contains 10mg Rosuvastatin (as calcium salt)

Roxatin Tablet 20mg
Each film coated tablet contains 20mg Rosuvastatin (as calcium salt)

DESCRIPTION

Roxatin Tablet 10 mg
Round (7 mm), light brick red biconvex film-coated tablet with Pharmaniaga icon on one side and plain on the other.

Roxatin Tablet 20mg
Round (9.5 mm), light brick red, biconvex film-coated tablet with Pharmaniaga icon on one side and plain on the other.

PHARMACODYNAMICS

Rosuvastatin is a selective, potent and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. Triglycerides (TG) and cholesterol in the liver are incorporated, with apolipoprotein B (ApoB), into very low density lipoprotein (VLDL) and released into the plasma for delivery to peripheral tissues. VLDL particles are TG-rich. Cholesterol-rich low density lipoprotein (LDL) is formed from VLDL and is cleared primarily through the high affinity LDL receptor in the liver.
Rosuvastatin produces its lipid-modifying effect in two ways; it increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

High density lipoprotein (HDL), which contains ApoA-I is involved, amongst other things, in transport of cholesterol from tissues back to the liver (reverse cholesterol transport).

The involvement of LDL-C in atherogenesis has been well documented. High LDL-C, TG, low HDL-C and ApoA-I have been linked to a higher risk of cardiovascular disease. Available data have shown the benefits on mortality and CV event rates of lowering LDL-C and TG or raising HDL-C. More recent data has linked the beneficial effects of HMG-CoA reductase inhibitors to lowering of non-HDL (i.e. all circulating cholesterol not in HDL) and ApoB or reducing the ApoB/ApoA-I ratio.

PHARMACOKINETICS

Absorption
Peak plasma concentrations of Rosuvastatin were reached 3 to 5 hours following oral dosing. Both peak concentration (C_{max}) and area under plasma concentration-time curve (AUC) increased in approximate proportion to Rosuvastatin dose. The absolute bioavailability of Rosuvastatin is approximately 20%.
Administration of Rosuvastatin with food decreased the rate of drug absorption by 20% as assessed by C_{max}, but there was no effect on the extent of absorption as assessed by AUC.

Plasma concentrations of Rosuvastatin do not differ following evening or morning drug administration.

Significant LDL-C reductions are seen when Rosuvastatin is given with or without food, and regardless of the time of day of drug administration.

Distribution
Mean volume of distribution at steady-state of Rosuvastatin is approximately 134 litres. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.

Metabolism
Rosuvastatin is not extensively metabolised; approximately 10% of a radio-labelled dose is recovered as metabolite. The major metabolite is N-desmethyl Rosuvastatin, which is formed principally by cytochrome P450 2C9, and N-desmethyl Rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of Rosuvastatin. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by Rosuvastatin.

Excretion
Following oral administration, Rosuvastatin and its metabolite are primarily excreted in the faeces (90%). The elimination half-life ($t_{1/2}$) of Rosuvastatin is approximately 19 hours.

After intravenous dose, approximately 28% of total body clearance was via the renal route and 72% by the hepatic route.

INDICATIONS

Rosuvastatin is indicated as an adjunct to diet, at least equivalent to the Adult Treatment Panel III (ATP III TLC diet), for the reduction of elevated total cholesterol, LDL-cholesterol, ApoB, the total cholesterol: HDL-cholesterol ratio and triglycerides and for increasing HDL-C, in hyperlipidemic and dyslipidemic conditions, when response to diet and exercise alone has been inadequate including:

Prevention 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 hsCRP level, age, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, Rosuvastatin is indicated to reduce total mortality and the risk of major cardiovascular events (cardiovascular death, stroke, MI, unstable angina, or arterial revascularization).
Rosuvastatin is indicated as an adjunct to diet for the treatment of patients with primary dysbetalipoproteinemia (Type III Hyperlipoproteinemia).

Primary hypercholesterolaemia (Type IIa including heterozygous familial hypercholesterolaemia and severe non-familial hypercholesterolaemia).

Combined (mixed) dyslipidemia (Type IIb).

Homozygous familial hypercholesterolaemia where Rosuvastatin is used either alone or as an adjunct to diet and other lipid lowering treatment such as apheresis.
Rosuvastatin is indicated as adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower Total-C and LDL-C to target levels.

Pediatric Patients 10 to 17 years of age with Heterozygous Familial Hypercholesterolemia (HeFH): Adjunct to diet to reduce Total-C, LDL-C and ApoB levels in adolescent boys and girls, who are at least one year post-menarche,10-17 years of age with heterozygous familial hypercholesterolaemia if after an adequate trial of diet therapy the following findings are present:

LDL-C > 190 mg/dL or > 160 mg/dL and there is a positive family history of premature cardiovascular disease (CVD) or two or more other CVD risk factors.

RECOMMENDED DOSAGE

Patients should be placed on a standard cholesterol-lowering diet (at least equivalent to the Adult Treatment Panel III (ATP III TLC diet)) before receiving Rosuvastatin, and should continue on this diet during treatment with Rosuvastatin. If appropriate, a program of weight control and physical exercise should be implemented.

Prior to initiating therapy with Rosuvastatin secondary causes for elevations in plasma lipid levels should be excluded. A lipid profile should also be performed. After initiation or upon titration of Rosuvastatin, lipid levels should be analyzed within 2-4 weeks and the dosage adjusted accordingly.

The usual recommended starting dosage of Rosuvastatin is 10 mg once daily. However, initiation of therapy with 5 mg once daily should be considered for special patient populations or patients requiring less aggressive LDL-C reductions. The choice of starting dose should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions. Rosuvastatin may be taken in the morning or evening, with or without food. The majority of patients are controlled at the 10 mg dose.

However, if necessary, dose adjustments to the next dose level can be made after 4-week intervals. The maximum response is usually achieved within 2-4 weeks and is maintained during chronic therapy. Increasing the dose to 40 mg should be reserved for patients with severe hypercholesterolaemia at high cardiovascular risk, (in particular those with familial hypercholesterolaemia), who do not achieve their treatment goal on 20 mg and should only be initiated under specialist supervision (see Warnings and Precautions) . The physician who elects to use Rosuvastatin at a dose higher than 20 mg should periodically re-evaluate the long-term risk/benefit of Rosuvastatin for the individual patient. Rosuvastatin should be prescribed with caution in patients with pre-disposing factors for myopathy / rhabdomyolysis.

The dosage of Rosuvastatin should be individualised according to baseline LDL-C, total-C/HDL-C ratio and/or TG levels, the recommended target lipid values and the patient response.

Lipid levels should be monitored periodically and, if necessary, the dose of Rosuvastatin adjusted based on target lipid levels recommended by guidelines

Dosage in patients with renal insufficiency
The usual dose range applies in patients with mild to moderate renal impairment.

The use of Rosuvastatin Calcium in patients with severe renal impairment is contraindicated.

Dosage in patients with hepatic insufficiency
There was no increase in systemic exposure to Rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, increased systemic exposure has been observed in subjects with Child-Pugh scores of 8 and 9. In these patients an assessment of renal function should be considered. There is no experience in subjects with Child-Pugh scores above 9. Rosuvastatin calcium is contraindicated in patients with active liver disease.

Use In elderly
The overall frequency of adverse events and types of adverse events were similar in patients above and below 65 years of age. The efficacy of Rosuvastatin in the geriatric population (≥65 years of age) was comparable to the efficacy observed in the non-elderly.

Pediatric patients (10 to 17 years of age)
In pediatric patients (10 to 17 years of age) with heterozygous familial hypercholesterolaemia the usual dose range of Rosuvastatin is 5-20 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualised according to the recommended goal therapy. Adjustments should be made at intervals of 4 weeks or more.

Use in children below 10 years
The safety and effectiveness in children have not been established. In children and adolescents with homozygous familial hypercholesterolemia experience is limited to eight patients (aged 8 years and above).

Dose on Asian patients
Initiation of Rosuvastatin calcium therapy with 5 mg once daily should be considered for Asian patients. The potential for increased systemic exposures relative to Caucasians is relevant when considering escalation of dose in cases where hypercholesterolaemia is not adequately controlled at doses of 5, 10 or 20 mg once daily.

Genetic polymorphisms
Specific types of genetic polymorphisms are known that can lead to increased Rosuvastatin exposure (see Pharmacokinetic Properties). For patients who are known to have such specific types of polymorphisms, a lower daily dose of Rosuvastatin is recommended.

Dosage in patients with pre-disposing factors to myopathy
The recommended start dose is 5 mg in patients with predisposing factors to myopathy.

Concomitant therapy
Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when Rosuvastatin is administered concomitantly with certain medicinal products 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). Whenever possible, alternative medications should be considered, and, if necessary, consider temporarily discontinuing Rosuvastatin therapy. In situations where co-administration of these medicinal products with Rosuvastatin is unavoidable, the benefit and the risk of concurrent treatment and Rosuvastatin dosing adjustments should be carefully considered.

Roxatin Tablet 10mg and Roxatin Tablet 20mg are not able to deliver all approved dose regimens of Rosuvastatin. Therefore, other approved dosage forms and strengths of rosuvastatin should be used in such cases.

ROUTE OF ADMINISTRATION

Oral.

CONTRAINDICATIONS

Rosuvastatin is contraindicated:
- in patients with hypersensitivity to any component of this product.
- in patients with active liver disease including unexplained, persistent elevations of serum transaminases and any spectrum transaminase elevation exceeding 3x the upper limit of normal (ULN).
- during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures.
- in patients with myopathy.
- in patients receiving concomitant cyclosporine

WARNINGS AND PRECAUTIONS

Roxatin Tablet is not recommended to be divided, broken or crushed.

Renal effects
Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of Rosuvastatin, 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. An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

Renal impairment
Rosuvastatin exposure is not influenced by mild to moderate renal impairment (CLcr ≥ 30mL/min/1.73m²). Exposure to Rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment (CLcr <30 mL/min/1.73m²)who are not receiving hemodialysis and dose adjustment is required.

Skeletal muscle effects
Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of Rosuvastatin and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of Rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of such combinations.

Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in Rosuvastatin-treated patients with all doses and in particular with doses > 20 mg. Very rare cases of rhabdomyolysis have been reported with the use of ezetimibe in combination with HMG-CoA reductase inhibitors. A pharmacodynamic interaction cannot be excluded and caution should be exercised with their combined use.As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis associated with Rosuvastatin use is higher at the 40 mg dose.

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
Rosuvastatin, as with other HMG-CoA reductase inhibitors, 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.
- 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) treat should not be started.

Whilst on 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 returns to normal, then consideration should be given to re-introducing Rosuvastatin or 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 very rare reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with statins, including Rosuvastatin. IMNM is clinically characterised by:
- persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statins treatment;.
- muscle biopsy showing necrotizing myopathy without significant inflammation;
- improvement with immunosuppressive agents.

The incidence of myositis and myopathy were reported in patients receiving other HMG-CoA reductase inhibitors together with fibric acid derivatives including gemfibrozil, ciclosporin, nicotinic acid, azole antifungals, protease inhibitors and macrolide antibiotics. Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of Rosuvastatin and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of Rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of such combinations. Rosuvastatin 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).

Liver Effects
As with other HMG-CoA reductase inhibitors, Rosuvastatin should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease.

It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of treatment. Rosuvastatin should 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) is higher at the 40 mg dose.

In patients with secondary hypercholesterolaemia, caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with Rosuvastatin.

Race
Pharmacokinetic studies show an increase in exposure in Asian patients compared with Caucasians.

Protease inhibitors
Increased systemic exposure to Rosuvastatin has been observed in patients receiving Rosuvastatin concomitantly with various protease inhibitors in combination with ritonavir. Consideration should be given both to the benefit of lipid lowering by use of Rosuvastatin in HIV patients receiving protease inhibitors and the potential for increased Rosuvastatin plasma concentrations when initiating and up titrating Rosuvastatin doses in patients treated with protease inhibitors. The concomitant use with certain protease inhibitors is not recommended unless the dose of Rosuvastatin is adjusted.

Lactose Intolerance
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Diabetes Mellitus
Some evidence suggests that statins as a class raise blood glucose and, in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/l, BMI >30 kg/m², raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Pediatric Patients (10 to 17 years of age)
The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in pediatric patients taking Rosuvastatin is limited to a one year period.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
There is no evidence of a sedative effect of Rosuvastatin. From the safety profile, Rosuvastatin is not expected to adversely affect the ability to drive or use machines.

INTERACTIONS WITH OTHER MEDICAMENTS
Effect of co-administered medicinal products on Rosuvastatin:

Transporter protein inhibitors: Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of Rosuvastatin with medicinal products that are inhibitors of these transporter proteins may result in increased Rosuvastatin plasma concentrations and an increased risk of myopathy.

Ciclosporin:
Rosuvastatin increased Rosuvastatin exposure and may result in increased risk of myopathy (see Table 3). Therefore, in patients taking ciclosporin, the dose of Rosuvastatin should not exceed 5 mg once daily.

Protease Inhibitors:
Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase Rosuvastatin exposure (see Table 3). Co-administration of 10 mg Rosuvastatin and a combination product of two protease inhibitor (300 mg atazanavir/ 100 mg ritonavir) was associated with an approximately three-fold and seven-fold increase in Rosuvastatin AUC and Cmax respectively. The concomitant use of Rosuvastatin and some protease inhibitor combinations may be considered after careful consideration of Rosuvastatin dose adjustments based on the expected increase in Rosuvastatin exposure.

Gemfibrozil and other lipid-lowering products: Concomitant use of Rosuvastatin and gemfibrozil resulted in a 2-fold increase in Rosuvastatin Cmax and AUC. No pharmacokinetic relevant interaction with fenofibrate is expected, however pharmacodynamic interaction may occur. Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (> or equal to 1g/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. These patients should also start with the 5 mg dose.

Ezetimibe: Concomitant use of 10 mg Rosuvastatin and 10 mg ezetimibe resulted in a 1.2 fold increase in AUC of Rosuvastatin in hypercholesterolaemic subjects. A pharmacodynamic interaction, in terms of adverse effects, between Rosuvastatin and ezetimibe cannot be ruled out.

Antacid: The simultaneous dosing of Rosuvastatin with an antacid suspension containing aluminium and magnesium hydroxide resulted in decrease in Rosuvastatin plasma concentration of approximately 50%. This effect was mitigated when the antacid was dosed 2 hours after Rosuvastatin. The clinical relevance of this interaction has not been studied.

Fusidic Acid: Interaction studies with Rosuvastatin and fusidic acid have not been conducted. As with other statins, muscle related events, including rhabdomyolysis, have been reported with Rosuvastatin and fusidic acid given concurrently. Patients should be closely monitored and temporary suspension of Rosuvastatin treatment may be appropriate.

Erythromycin: Concomitant use of Rosuvastatin and erythromycin resulted in a 20% decrease in AUC (0-t) 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:
Rosuvastatin is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes. In addition, Rosuvastatin is a poor substrate for these isoenzymes. Therefore, drug 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 also Table 3):
When it is necessary to co-administer Rosuvastatin with other medicinal products known to increase exposure to Rosuvastatin, doses of Rosuvastatin should be adjusted. Start with a 5 mg once daily dose of Rosuvastatin if the expected increase in exposure (AUC) is approximately 2-fold or higher.

The maximum daily dose of Rosuvastatin should be adjusted so that the expected Rosuvastatin exposure would not likely exceed that of the recommended maximum daily dose of Rosuvastatin taken without interacting medicinal products. For example, where the recommended dose of Rosuvastatin is 20mg; the dose of Rosuvastatin taken with a ritonavir/atazanavir combination (3.1-fold increase) should not exceed 5 mg, and the dose of Rosuvastatin taken with gemfibrozil (1.9-fold increase) should not exceed to 10 mg.

Table 3: Effect of co-administered medicinal products on Rosuvastatin exposure (AUC; in order of decreasing magnitude)

Interacting drug dose regimen	Rosuvastatin dose regimen	Change in Rosuvastatin AUC*
Ciclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 10 days	7.1-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 ↑
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[3]	20 mg, single dose[3]	2-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1.9-fold ↑
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, single dose	**1.4-fold ↑
Ezetimibe 10 mg OD, 14 days	10 mg, OD, 14 days	**1.2-fold ↑
Fosamprenavir 700 mg / ritonavir 100 mg BID, 8 days	10 mg, single dose	↔
Aleglitazar 0.3 mg, 7 days	40 mg, 7 days	↔
Silymarin 140 mgTID, 5 days	10 mg, single dose	↔
Fenofibrate 67 mg TID, 7 days	10 mg, 7 days	↔
Rifampin 450 mg OD, 7 days	20 mg, single dose	↔
Ketoconazole 200 mg BID, 7 days	80 mg, single dose	↔
Fluconazole 200 mg OD, 11 days	80 mg, single dose	↔
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 " ", no change as " ", decrease as " ".
**The table shows the most significant ratio
OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily

Other medications:
Concurrent use of fibrates may cause severe myositis and myoglobinuria.
Effect of Rosuvastatin on co-administered medicinal products:

Vitamin K antagonists: As with HMG CoA reductase inhibitors, the initiation of treatment or dosage up-titration of Rosuvastatin in patients treated concomitantly with vitamin K antagonist (e.g. warfarin or another coumarin anticoagulant) may result in an increase in International Normalised Ratio (INR). Discontinuation or down-titration of Roxatin Tablet may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.

Oral contraceptive/hormone replacement therapy (HRT): Concomitant use of Rosuvastatin and an oral contraceptive resulted in an increase in ethinyl estradiol and norgestrel AUC of 26% and 34% respectively. These increased plasma levels should be considered when selecting oral contraceptive doses. There are no pharmacokinetic data available in patients taking concomitant Rosuvastatin and HRT and therefore a similar effect cannot be excluded. However, the combination has been extensively used in women in clinical trials and was well tolerated.

Other medicinal products: No clinically relevant interaction with digoxin is expected.

Paediatric population: The extent of interactions in the paediatric population is not known.

PREGNANCY AND LACTATION
The safety of Rosuvastatin during pregnancy and whilst breast-feeding has not been established. Women of child-bearing potential should use appropriate contraceptive measures.

ADVERSE EFFECTS
There have been rare reports of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These issues have been reported for all statins. The reports are generally non-serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median 3 weeks).
Increases with HbA1c and fasting blood glucose have been reported with statins. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.
The adverse reactions seen with Rosuvastatin are generally mild and transient.

Tabulated list of adverse reactions

System organ class	Frequency	Undesirable effect
Blood and lymphatic system disorders	Rare	Thrombocytopenia
Immune system disorders	Rare	Hypersensitivity reactions including angioedema
Endocrine disorders	Common	Diabetes mellitus1
Psychiatric disorders	Not known	Depression
Nervous system disorders	Common	Headache Dizziness
	Very rare	Polyneuropathy Memory loss
	Not known	Peripheral neuropathy Sleep disturbances (including insomnia and nightmares)
Respiratory, thoracic and mediastinal disorders	Not known	Cough Dyspnoea
Gastrointestinal disorders	Common	Constipation Nausea Abdominal pain
	Rare	Pancreatitis
	Not known	Diarrhoea
Hepatobiliary disorders	Rare	Increased hepatic transaminases
	Very rare	Jaundice Hepatitis
Skin and subcutaneous tissue disorders	Uncommon	Pruritus Rash Urticaria
	Not known	Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders	Common	Myalgia
	Rare	Myopathy (including myositis) Rhabdomyolysis
	Very rare	Arthralgia
	Not known	Immune-mediated necrotising myopathy
Renal and urinary disorders	Very rare	Haematuria
Reproductive system and breast disorders	Very rare	Gynaecomastia
General disorders and administration site conditions	Common	Asthenia
	Not known	Oedema

[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).

As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to be dose dependent.

Renal effects
Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with Rosuvastatin. Shifts in urine protein from none or trace to ++ or more were seen in patients at some time during treatment with 10 and 20 mg, and 40 mg. A minor increase in shift from none or trace to + was observed with the 20 mg dose. In most cases, proteinuria decreases or disappears spontaneously on continued therapy. Available data has not identified a causal association between proteinuria and acute or progressive renal disease.

Haematuria has been observed in patients treated with Rosuvastatin but clinical trial data show that the occurrence is low.

Skeletal muscle effects
Effects on skeletal muscle e.g. myalgia, myopathy (including myositis) and, rarely, rhabdomyolysis with and without acute renal failure have been reported in Rosuvastatin-treated patients with all doses and in particular with doses > 20 mg.

A dose-related increase in CK levels has been observed in patients taking Rosuvastatin; the majority of cases were mild, asymptomatic and transient. If CK levels are elevated (>5xULN), treatment should be discontinued.

Liver effects
As with other HMG-CoA reductase inhibitors, a dose-related increase in transaminases has been observed in a small number of patients taking Rosuvastatin; majority of cases were mild, asymptomatic and transient.
The following adverse events have been reported with some statins:
- Sexual dysfunction.
- Exceptional cases of interstitial lung disease, especially with long term therapy.
- Tendon disorders, sometimes complicated by rupture.

The reporting rates for rhabdomyolysis, serious renal events and serious hepatic events (consisting mainly of increased hepatic transaminases) is higher at the 40 mg dose.

OVERDOSE AND TREATMENT
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. Hemodialysis is unlikely to be of benefit.

STORAGE CONDITION
Store below 30°C. Store in the original package.

SHELF LIFE
Product should not be used beyond the expiry date imprinted on the product packaging.

DOSAGE FORMS AND PACKAGING AVAILABLE
In box of 30's (3 blisters x 10 tablets)

Product Registration Holder/manufacturer:
Pharmaniaga Manufacturing Berhad (198001006232)
No. 11A, Jalan P/1, Kawasan Perusahaan Bangi,
43650 Bandar Baru Bangi, Selangor Darul Ehsan,
Malaysia.

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