

PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

Rosuvastatin Sandoz 10 mg film-coated tablets

Rosuvastatin Sandoz 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Rosuvastatin Sandoz 10 mg film-coated tablets

Each film-coated tablet contains 10 mg rosuvastatin (as rosuvastatin calcium).

Each film-coated tablet contains 52.92 mg lactose anhydrous.

Rosuvastatin Sandoz 20 mg film-coated tablets

Each film-coated tablet contains 20 mg rosuvastatin (as rosuvastatin calcium).

Each film-coated tablet contains 105.84 mg lactose anhydrous.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Rosuvastatin Sandoz 10 mg film-coated tablets

Brown, round, film-coated tablets with "RSV 10" debossed on one side.

Rosuvastatin Sandoz 20 mg film-coated tablets

Brown, round, film-coated tablets with "RSV 20" debossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 e.g., an elevated hsCRP level, age, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, Rosuvastatin Sandoz is indicated to reduce total mortality and the risk of major cardiovascular events [cardiovascular death, stroke, myocardial infarction (MI), unstable angina, or arterial revascularization].

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 Sandoz is used either alone or as an adjunct to diet, and other lipid-lowering treatment e.g., apheresis.

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 hypercholesterolemia 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.

4.2 Posology and method of administration

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

Prior to initiating therapy with Rosuvastatin Sandoz, 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 Sandoz, lipid levels should be analyzed within 2 - 4 weeks and the dosage adjusted accordingly.

Usual Recommended Starting Dose: 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 patients' cholesterol level and future cardiovascular risk, as well as the potential risk for adverse reactions. It 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 *Special Warnings and Precautions for Use*). The physician who elects to use Rosuvastatin Sandoz at a dose higher than 20 mg should periodically re-evaluate the long-term risk/benefit of Rosuvastatin Sandoz for the individual patient.

Rosuvastatin Sandoz should be prescribed with caution in patients with predisposing factors for myopathy/rhabdomyolysis (see *Special Warnings and Precautions for Use*).

The dosage of Rosuvastatin Sandoz 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 Sandoz should be 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 Sandoz 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 Sandoz is contraindicated in patients with active liver disease.

Use in the 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 hypercholesterolemia the usual dose range of Rosuvastatin Sandoz 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 individualized according to the recommended goal of 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 (aged 8 years and above).

Dosage on Asian Patients

Initiation of Rosuvastatin Sandoz 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. For patients who are known to have such specific types of polymorphisms, a lower daily dose of Rosuvastatin Sandoz is recommended.

Dosage in patients with pre-disposing factors to myopathy

The recommended start dose is 5 mg in patients with pre-disposing 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. 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 Sandoz 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.

Method of administration

For oral use.

4.3 Contraindications

Rosuvastatin Sandoz is contraindicated:

- in patients with hypersensitivity to rosuvastatin or to any of the excipients.
- in patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3x the upper limit of normal (ULN).
- in patients with severe renal impairment (creatinine clearance <30 ml/min).
- in patients with myopathy.
- in patients receiving concomitant ciclosporin.
- during pregnancy and lactation and in women of child-bearing potential not using appropriate contraceptive measures.

The 40 mg dose is contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis.

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
- alcohol abuse
- situations where an increase in plasma levels may occur
- Asian patients
- concomitant use of fibrates

4.4 Special warnings and precautions for useRenal 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 (see section 4.8). The reporting rate for serious renal events in post-marketing use is higher at the 40 mg dose. An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

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 (see section 4.5) and caution should be exercised with their combined use. As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis associated with rosuvastatin in post-marketing 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 (> 5x ULN) a confirmatory test should be carried out within 5 - 7 days. If the repeat test confirms a baseline CK > 5x ULN, treatment should not be started.

Before Treatment

Rosuvastatin Sandoz, 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 (> 5x ULN) treatment 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 (> 5x ULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤ 5x ULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing Rosuvastatin Sandoz 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 very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with statins, including rosuvastatin. IMNM is clinically characterized by:

- persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment;
- muscle biopsy showing necrotizing myopathy without significant inflammation;
- improvement with immunosuppressive agents.

There was no evidence of increased skeletal muscle effects in the small number of patients dosed with

rosuvastatin and concomitant therapy. However, an increase in the incidence of myositis and myopathy has been seen 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. The 40 mg dose is contraindicated with concomitant use of a fibrate.

Rosuvastatin 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. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.

Statin therapy may be re-introduced seven days after the last dose of fusidic acid.

In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of rosuvastatin and fusidic acid should only be considered on a case by case basis and under close medical supervision.

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) in post-marketing use 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 subjects compared with Caucasians.

Protease inhibitors

Increased systemic exposure to rosuvastatin has been observed in subjects 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.

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.

In patients with fasting glucose 5.6 to 6.9 mmol/L, treatment with rosuvastatin has been associated with an increased risk of diabetes mellitus.

Myasthenia Gravis/ Ocular Myasthenia

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia. Rosuvastatin Sandoz should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

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.

Special warnings regarding excipients

Rosuvastatin Sandoz contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

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

During concomitant treatment with rosuvastatin and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers. Rosuvastatin is contraindicated in patients receiving concomitant ciclosporin (see section 4.3). Concomitant administration did not affect plasma concentrations of ciclosporin.

Protease inhibitors

Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure. Co-administration of 10 mg rosuvastatin and a combination product of two protease inhibitors (300 mg atazanavir / 100 mg ritonavir) in healthy volunteers was associated with an approximately three-fold and seven-fold increase in rosuvastatin steady-state AUC and C_{max} 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 C_{max} and AUC.

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 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. The 40 mg dose is contraindicated with concomitant use of a fibrate. These patients should also start with the 5 mg dose.

Concurrent use of fibrates may cause severe myositis and myoglobinuria.

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 a 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 in post-marketing experience 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 C_{max} 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, 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)

When it is necessary to co-administer rosuvastatin with other medicinal products known to increase exposure to rosuvastatin, doses of rosuvastatin should be adjusted. It is recommended that prescribers consult the relevant product information when considering administration of such products together with rosuvastatin.

If medicinal product is observed to increase rosuvastatin AUC approximately 2-fold or higher, the starting dose of rosuvastatin should not exceed 5 mg once daily. The maximum daily dose of rosuvastatin should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of rosuvastatin taken without interacting medicinal products, for example a 20 mg dose of rosuvastatin with gemfibrozil (1.9-fold increase), and a 10 mg dose of rosuvastatin with combination atazanavir/ritonavir (3.1-fold increase).

If medicinal product 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 rosuvastatin dose above 20mg.

Protease Inhibitors: Co-administration of rosuvastatin with certain protease inhibitors or combination of protease inhibitors may increase the rosuvastatin exposure, (AUC) up to 7-fold. Dose adjustment are needed depending on the level of effect on rosuvastatin exposure.

Table - Effect of co-administered medicinal products on rosuvastatin exposure (AUC; in order of decreasing magnitude) from published clinical trials		
2-fold or greater than 2-fold increase in AUC of rosuvastatin		
Interacting drug 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	7.39-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	2.69-fold ↑
Ombitasvir 25 mg/paritaprevir 150 mg/ ritonavir 100 mg/ dasabuvir 400 mg BID	5 mg, single dose	2.59-fold ↑
Teriflunomide	Not available	2.5-fold ↑
Grazoprevir 200 mg/elbasvir 50 mg OD	10 mg, single dose	2.26-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 ↑
Capmatinib 400 mg BID	10 mg, single dose	2.1-fold ↑
Clopidogrel 300 mg loading, followed by 75 mg at 24 hours	20 mg, single dose	2-fold ↑
Fostamatinib 100 mg twice daily	20 mg, single dose	2.0-fold ↑
Febuxostat 120 mg OD	10 mg, single dose	1.9-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1.9-fold ↑
Less than 2-fold increase in AUC of rosuvastatin		
Interacting drug 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, 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 drug 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 rosuvastatin 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		

The following medical product/combinations did not have a clinically significant effect on the AUC ratio of rosuvastatin at co-administration:
Aleglitazar 0.3 mg 7 days dosing; Fenofibrate 67 mg 7 days TID dosing; Fluconazole 200 mg 11 days OD dosing; Fosamprenavir 700 mg/ritonavir 100 mg 8 days BID dosing; Ketoconazole 200 mg 7 days BID dosing; Rifampin 450 mg 7 days OD dosing; Silymarin 140 mg 5 days TID dosing.

Effect of rosuvastatin on co-administered medicinal products

Vitamin K antagonists

As with other HMG-CoA reductase inhibitors, the initiation of treatment or dosage up-titration of rosuvastatin in patients treated concomitantly with vitamin K antagonists (e.g. warfarin or another coumarin anticoagulant) may result in an increase in International Normalised Ratio (INR). Discontinuation or down-titration of rosuvastatin 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 subjects 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

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, rosuvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment. **Also see section 4.4.**

Paediatric population

Interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known.

4.6 Fertility, pregnancy and lactation

Rosuvastatin is contraindicated in pregnancy and lactation.

Women of child bearing potential should use appropriate contraceptive measures.

Since cholesterol and other products of cholesterol biosynthesis are essential for the development of the foetus, the potential risk from inhibition of HMG-CoA reductase outweighs the advantage of treatment during pregnancy. Animal studies provide limited evidence of reproductive toxicity. If a patient becomes pregnant during use of this product, treatment should be discontinued immediately.

Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion in milk in humans.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

4.8 Undesirable effects

There have been rare post-marketing reports of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive 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 in 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 events seen with Rosuvastatin Sandoz are generally mild and transient.

List of adverse reactions

Adverse reactions listed below are classified according to frequency and system organ class (SOC).

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), myasthenia gravis

Eye disorders

Not known: Ocular myasthenia

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, drug reaction with eosinophilia and systemic symptoms (DRESS)

Musculoskeletal and connective tissue disorders

Common: Myalgia

Rare: Myopathy (including myositis), rhabdomyolysis

Very rare: Arthralgia

Not known: Immune-mediated necrotizing 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 $<1\%$ of patients at some time during treatment with 10 and 20 mg, and in approximately 3% of patients treated with 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. Review of data from clinical trials and post-marketing experience to date has not identified a causal association between proteinuria and acute or progressive renal disease.

Haematuria has been observed in patients treated with rosuvastatin and 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 ($> 5x$ ULN), 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; the 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.

Pediatric patients 10 to 17 years of age

The safety and tolerability profile of rosuvastatin 5 to 20 mg daily was generally similar to that of placebo. However, elevations in serum creatine phosphokinase (CK) $>10 \times$ ULN were observed more frequently in rosuvastatin compared with placebo-treated children.

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

Pharmacotherapeutic group: Lipid modifying agent, plain, HMG-CoA reductase inhibitors

ATC code: C10A A07

Mechanism of action

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 for 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 effects 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. Epidemiological studies have established that high LDL-C, TG, low HDL-C and ApoA-I have been linked to a higher risk of cardiovascular disease. Intervention studies 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.

Pharmacodynamic effects

Rosuvastatin reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I (see Table 1 and 2).

Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the 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.

Table 1: Dose response in patients with primary hypercholesterolaemia (Type IIa and IIb) (Adjusted mean percent change from baseline)

Dose	N	LDL-C	Total-C	HDL-C	TG	nonHDL- C	ApoB	ApoA-I
Placebo	13	-7	-5	3	-3	-7	-3	0
5	17	-45	-33	13	-35	-44	-38	4
10	17	-52	-36	14	-10	-48	-42	4
20	17	-55	-40	8	-23	-51	-46	5
40	18	-63	-46	10	-28	-60	-54	0

Table 2: Dose response in patients with Hypertriglyceridaemia (Type IIb or Type IV) (Median % change from baseline)

Dose	N	TG	LDL-C	Total-C	HDL-C	nonHDL- C	VLDL-C	VLDL-TG
Placebo	26	1	5	1	-3	2	2	6
5	25	-21	-28	-24	3	-29	-25	-24
10	23	-37	-45	-40	8	-49	-48	-39
20	27	-37	-31	-34	22	-43	-49	-40

40	25	-43	-43	-40	17	-51	-56	-48
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Clinical efficacy

Rosuvastatin is effective in adults with hypercholesterolaemia, with and without hypertriglyceridaemia, regardless of race, sex or age and in special populations such as diabetics, or patients with familial hypercholesterolaemia.

5.2 Pharmacokinetic properties

Absorption

Peak plasma concentrations of rosuvastatin were reached 3 to 5 hours following oral dosing. Both peak concentration (C_{max}) and area under the 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 radiolabelled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 2C9, and *in vitro* studies have demonstrated that 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 an intravenous dose, approximately 28% of total body clearance was via the renal route and 72% by the hepatic route.

Special populations

Age and sex: There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin.

Pediatric use: Patients treated with 5 mg, 10 mg and 20 mg daily rosuvastatin had an adverse experience profile generally similar to that of patients treated with placebo. Although not all adverse reactions identified in the adult population have been observed in clinical trials of children and adolescent patients, the same warnings and precautions for adults should be considered for children and adolescents. There was no detectable effect of rosuvastatin on growth, weight, BMI (body mass index), or sexual maturation in pediatric patients (10 to 17 years of age). Adolescent females should be counseled on appropriate contraceptive methods while on rosuvastatin therapy. Rosuvastatin has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age. Doses of rosuvastatin greater than 20 mg have not been studied in the pediatric population.

In children and adolescents with homozygous familial hypercholesterolemia experience is limited (aged 8 years and above).

Genetic polymorphisms: Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, involves OATP1B1 and BCRP transporter proteins. In patients with SLCO1B1 (OATP1B1) and/or ABCG2 (BCRP)

genetic polymorphisms there is a risk of increased rosuvastatin exposure. Individual polymorphisms of SLCO1B1 c.521CC and ABCG2 c.421AA are associated with an approximate 1.6-fold higher rosuvastatin exposure (AUC) compared to the SLCO1B1 c.521TT or ABCG2 c.421CC genotypes. This specific genotyping is not established in clinical practice, but for patients who are known to have these types of polymorphisms, a lower daily dose of rosuvastatin is recommended.

Race: Pharmacokinetic studies show an approximate 2-fold elevation in median AUC in Asian subjects compared with Caucasians. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups.

Patients with renal impairment: Mild to moderate renal impairment ($\text{CL}_{\text{Cr}} \geq 30 \text{ mL/min/1.73 m}^2$) had no influence on plasma concentrations of rosuvastatin. However, plasma concentrations of rosuvastatin increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment ($\text{CL}_{\text{Cr}} < 30 \text{ mL/min/1.73 m}^2$) not receiving hemodialysis compared with healthy subjects ($\text{CL}_{\text{Cr}} > 80 \text{ mL/min/1.73 m}^2$).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet contents

Anhydrous Lactose
Silica, Colloidal Anhydrous
Maize Starch
Silicified Microcrystalline Cellulose
Talc
Sodium Stearyl Fumarate

Tablet coating

Hypromellose
Mannitol
Macrogol 6000
Titanium dioxide
Ferric Oxide, Yellow
Ferric Oxide, Red
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Storage Condition

Store in the original package in order to protect from moisture.
Store below 30°C.

6.5 Nature and contents of container

28, 30 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precaution for disposal and other handling

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT REGISTRATION HOLDER

Sandoz Products Malaysia Sdn. Bhd.
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47400 Petaling Jaya, Selangor, Malaysia

8. DATE OF REVISION OF THE TEXT

Jul 2025