300 mm

210 mm

DXM-ROSUVASTATIN

Film Coated Tablet 10 mg or 20 mg

Dexa Jitadtee

Compositions:
DXM-ROSUVASTATIN FILM COATED TABLET 10 MG
Each film coated tablet contains
Rosuvastatin calcium equivalent to Rosuvastatin 10 mg

DXM-ROSUVASTATIN FILM COATED TABLET 20 MG
Each film coated tablet contains
Rosuvastatin calcium equivalent to Rosuvastatin 20 mg

Product Descriptions:
DXM-ROSUVASTATIN FILM COATED TABLET 10 MG
White, round, and shallow-biconvex tablet with diameter 7 mm. Marked 'DEXA' on side I, unmarked on side II.

DXM-ROSUVASTATIN FILM COATED TABLET 20 MG
White, round, and shallow-biconvex tablet with diameter 9 mm. Marked 'DEXA' on side I, unmarked on side II.

Pharmacology:
Pharmacotherapeutic group: 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.

Pharmacokinetics:
Absorption
In clinical pharmacology studies in man, 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 liters. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.
Metabolism
Rosuvastatin is not extensively metabolized; 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 feces (90%). The elimination half-life ($t_{½}$) 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
The safety and effectiveness of rosuvastatin in patients 10 to 17 years of age with heterozygous familial hypercholesterolemia were evaluated in a controlled clinical trial of 12 weeks duration followed by 40 weeks of open-label exposure. 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 prepubertal 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 to eight patients (aged 8 years and above).
In a pharmacokinetic study, 18 patients (9 boys and 9 girls) 10 to 17 years of age with heterozygous FH received single and multiple oral doses of rosuvastatin. Both C_{max} and AUC of rosuvastatin were similar to values observed in adult subjects administered the same doses.
Genetic polymorphism
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 (CrCl ≥30 ml/minute/1.73 m^2) had no influence on plasma concentration of rosuvastatin. However, plasma concentration of rosuvastatin increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment (CrCl <30 ml/minute/1.73 m^2) not receiving hemodialysis compared with healthy individuals (CrCl >80 ml/minute/1.73 m^2).

Indications:
DXM-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, DXM-Rosuvastatin is indicated to reduce total mortality and the risk of major cardiovascular events (cardiovascular death, stroke, MI, unstable angina, or arterial revascularization).
- DXM-Rosuvastatin is indicated as an adjunct to diet for the treatment of patients with primary dysbetalipoproteinemia (type III hyperlipoproteinemia).
- Primary hypercholesterolemia (type IIa including heterozygous familial hypercholesterolemia and severe non- familial hypercholesterolemia).
- Combined (mixed) dyslipidemia (type IIb).
- Homozygous familial hypercholesterolemia where DXM-Rosuvastatin is used either alone or as an adjunct to diet and other lipid lowering treatment such as apheresis.
- DXM-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 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.

Recommended Dose:
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 DXM-Rosuvastatin, and should continue on this diet during treatment with DXM-Rosuvastatin. If appropriate, a program of weight control and physical exercise should be implemented.
Prior to initiating therapy with DXM-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 DXM-Rosuvastatin, lipid levels should be analyzed within 2–4 weeks and the dosage adjusted accordingly.
The usual recommended starting dose of DXM-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. DXM-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 hypercholesterolemia at high cardiovascular risk (in particular those with familial hypercholesterolemia), 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 DXM-Rosuvastatin at a dose higher than 20 mg should periodically reevaluate the long-term risk/benefit of DXM-Rosuvastatin for the individual patient. DXM-Rosuvastatin should be prescribed with caution in patients with predisposing factors for myopathy/rhabdomyolysis (see **Warnings and Precautions**).
The dosage of DXM-Rosuvastatin should be individualized according to baseline LDL-C, total-C/HDL-C ratio, and/or TG levels, the recommended target lipid values (see **Recommendations for the Management and Treatment of Dyslipidemia [Canada] summarized below in Table 1**) and/or the Third Report of the U.S. National Cholesterol Education Program [NCEP Adult Treatment Panel III] and the patient response.

The majority (80%) of patients treated with rosuvastatin 10 mg achieved their NCEP ATP III treatment target for LDL-C levels; fewer patients (68%) achieved target on the 5 mg dose. The difference between rosuvastatin 5 mg and 10 mg was greatest for high risk subjects (40% versus 61%, respectively), i.e. for patients who have a lower LDL-C target.
Lipid levels should be monitored periodically and, if necessary, the dose of DXM-Rosuvastatin adjusted based on target lipid levels recommended by guidelines.

Table 1. Canadian Recommendation for Target Lipid Values Based on Level of Risk

Level of risk (definition)	Target values LDL-C (mmol/l)	Total-C/ HDL-C ratio	TG (mmol/l)
Very high* (10-year risk of CAD >30%, or history of cardiovascular disease or diabetes)	<2.5	<4.0	<2.0
High* (10-year risk CAD 20%–30%)	<3.0	<5.0	<2.0
Moderate** (10-year risk of CAD 10%–20%)	<4.0	<6.0	<2.0
Low*** (10-year risk of CAD <10%)	<5.0	<7.0	<3.0

*Start medication and lifestyle changes concomitantly if values are above target values
**Start medication if target values are not achieved after 3 months of lifestyle modification
***Start medication if target values are not achieved after 6 months of lifestyle modification

The following reductions in total cholesterol, LDL-C, TG, total-C/HDL and increases in HDL-C have been observed in a dose-response study, and may serve as a guide to treatment of patients with mild to moderate hypercholesterolemia:

Table 2. Dose-Response in Patients with Mild to Moderate Hypercholesterolemia (Mean Percent change from Baseline)

DXM-Rosuvastatin dose (mg/day)	N	Total-C	LDL-C	TG	HDL-C	Total-C/ HDL-C	Apo B
Placebo	13	-5	-7	-3	3	-8	-3
5	17	-33	-45	-35	13	-41	-38
10	17	-36	-52	-10	14	-43	-42
20	17	-40	-55	-23	8	-44	-46
40	18	-46	-63	-28	10	-51	-54

Dosage in patients with renal insufficiency
The usual dose range applies in patients with mild to moderate renal impairment. For patients with severe renal impairment (CrCl <30 ml/minute/1.73 m^2) not on hemodialysis, dosing of DXM-Rosuvastatin should be started at 5 mg once daily and should not exceed 10 mg once daily (see **Pharmacokinetics**).
Dosage in patients with hepatic insufficiency
There was no increase in systemic exposure to rosuvastatin in patients with Child-Pugh scores of 7 or below. However, increased systemic exposure has been observed in patients with Child-Pugh scores of 8 and 9. In these patients an assessment of renal function should be considered. There is no experience in patients with Child-Pugh scores above 9. DXM-Rosuvastatin is contraindicated in patients with active liver disease.
Use in the elderly
Of the 10,275 patients in clinical studies with rosuvastatin, 3,159 (31%) were 65 years and older, and 698 (6.8%) were 75 years and older. 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 DXM-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 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 to eight patients (aged 8 years and above).
Dosage on Asian patients
Initiation of DXM-Rosuvastatin 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 hypercholesterolemia is not adequately controlled at doses of 5, 10, or 20 mg once daily (see **Warnings and Precautions** and **Pharmacokinetics**).
Genetic polymorphisms
Specific types of genetic polymorphisms are known that can lead to increased rosuvastatin exposure (see **Pharmacokinetics**). For patients who are known to have such specific types of polymorphisms, a lower daily dose of DXM-Rosuvastatin is recommended.
Dosage in patients with predisposing factors to myopathy
The recommended starting dose is 5 mg in patients with predisposing factors to myopathy (see **Warnings and Precautions**).
Concomitant therapy
Rosuvastatin is a substrate of various transporter proteins (e.g., OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when DXM-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 DXM-Rosuvastatin therapy. In situations where coadministration of these medicinal products with DXM-Rosuvastatin is unavoidable, the benefit and the risk of concurrent treatment and DXM-Rosuvastatin dosing adjustments should be carefully considered. If concomitant use of DXM-Rosuvastatin with ciclosporin cannot be avoided, the dose of DXM-Rosuvastatin should not exceed 5 mg once daily (see **Warnings and Precautions** and **Interactions with Other Medicaments**).

Route of Administration:
Oral.

Contraindications:
- DXM-Rosuvastatin is contraindicated in patients with hypersensitivity to any component of this product.
- DXM-Rosuvastatin is contraindicated in 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).
- DXM-Rosuvastatin is contraindicated during pregnancy, while breastfeeding, and in women of childbearing potential not using appropriate contraceptive measures.
- DXM-Rosuvastatin is contraindicated in patients with myopathy.
- DXM-Rosuvastatin is contraindicated in patients receiving concomitant ciclosporin.

Warnings and Precautions:
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 a 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 (CrCl ≥30 ml/minute/1.73 m^2). Exposure to rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment (CrCl <30 ml/minute/1.73 m^2) who are not receiving hemodialysis and dose adjustment is required (see **Recommended Dose** and **Pharmacokinetics**).
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 **Interactions with Other Medicaments**) 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 postmarketing 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 (>5 x ULN) a confirmatory test should be carried out within 5–7 days. If the repeat test confirms a baseline CK >5 x ULN, treatment should not be started.
Before treatment
DXM-Rosuvastatin, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with predisposing 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 of 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 (>5 x 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 (>5 x ULN) or, if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤5 x ULN). If symptoms resolve and CK levels return to normal, then consideration should be given to reintroducing DXM-Rosuvastatin 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 some 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.

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In few cases, statins have been reported to induce *de novo* or aggravate preexisting myasthenia gravis or ocular myasthenia. DXM-Rosuvastatin should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.
In clinical trials, 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 DXM-Rosuvastatin and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of DXM-Rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of such combinations.
DXM-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, DXM-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. DXM-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 postmarketing use is higher at the 40 mg dose.
In patients with secondary hypercholesterolemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with DXM-Rosuvastatin.

Race
Pharmacokinetic studies show an increase in exposure in Asian compared with Caucasians (see **Recommended Dose** and **Pharmacokinetics**).

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 DXM-Rosuvastatin in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up titrating DXM-Rosuvastatin doses in patients treated with protease inhibitors. The concomitant use with certain protease inhibitors is not recommended unless the dose of DXM-Rosuvastatin is adjusted (see **Recommended Dose** and **Interactions with Other Medicaments**).

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 dyspnea, nonproductive 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 hyperglycemia 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/m^2, 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:
Pharmacology testing revealed 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 coadministered 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
Ciclosporin 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**). Coadministration of 10 mg rosuvastatin and a combination product of two protease inhibitors (300 mg atazanavir/100 mg ritonavir) in healthy individuals was associated with an approximately three-fold and seven-fold increase in rosuvastatin 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 (see **Warnings and Precautions**). 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 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 individuals with hypercholesterolemia (see **Table 3**). 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 postmarketing 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 **Table 3**)
When it is necessary to coadminister 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 the 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 5 mg dose of rosuvastatin with ciclosporin (7.1-fold increase in exposure), a 10 mg dose of rosuvastatin with ritonavir/atazanavir (3.1-fold increase), and a 20 mg dose of rosuvastatin with gemfibrozil (1.9-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 20 mg.
Protease inhibitors
Coadministration of rosuvastatin with certain protease inhibitors or combination of protease inhibitors may increase the rosuvastatin exposure, (AUC) up to 7-fold (see **Table 1**). Dose adjustments are needed depending on the level of effect on rosuvastatin exposure.

Table 3. Effect of Coadministered Medicinal Products on Rosuvastatin Exposure (AUC; in order of decreasing magnitude)

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 coadministration 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 medicinal product/combinations did not have a significant effect on the AUC ratio of rosuvastatin at coadministration:
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.

Other medications
Concurrent use of fibrates may cause severe myositis and myoglobinuria.

Effect of rosuvastatin on coadministered 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 Normalized 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 ethinylestradiol 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 and was well tolerated.
Other medicinal products
No clinically relevant interaction with digoxin is expected.
Pediatric population
Interaction studies have only been performed in adults. The extent of interactions in the pediatric population is not known.

Pregnancy and Lactation:
The safety of DXM-Rosuvastatin during pregnancy and whilst breastfeeding has not been established.
Women of childbearing potential should use appropriate contraceptive measures.

Adverse Effects:
There have been rare postmarketing 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 nonserious 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 reactions seen with rosuvastatin are generally mild and transient.
The following list presents the adverse reaction profile for rosuvastatin. Adverse reactions listed below are classified according to frequency and system organ class (SOC).
The frequencies of adverse reactions are ranked according to the following: common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated).
Blood and lymphatic system disorders
- *Rare:* thrombocytopenia.

Immune system disorders
- *Rare:* hypersensitivity reactions including angioedema.

Endocrine disorders
- *Common:* diabetes mellitus (frequency will depend on the presence or absence of risk factors; fasting blood glucose ≥5.6 mmol/l, BMI >30 kg/m^2 raised triglycerides, history of hypertension).

Psychiatric disorders
- *Not known:* depression.

Nervous system disorders
- *Common:* headache, dizziness.
- *Very rare:* polyneuropathy, memory loss.
- *Not known:* sleep disturbances (including insomnia and nightmares), peripheral neuropathy, myasthenia gravis.

Eye disorders
- *Not known:* ocular myasthenia.

Respiratory, thoracic, and mediastinal disorders
- *Not known:* cough, dyspnea.

Gastrointestinal disorders
- *Common:* constipation, nausea, abdominal pain.
- *Rare:* pancreatitis.
- *Not known:* diarrhea.

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:* hematuria.

Reproductive system and breast disorders
- *Very rare:* gynecomastia.

General disorders and administration site conditions
- *Common:* asthenia.
- *Not known:* edema.

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. No causal association between proteinuria and acute or progressive renal disease.
Hematuria has been observed in patients treated with rosuvastatin and 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 (>5 x ULN), treatment should be discontinued (see **Warnings and Precautions**).

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
In a 12-week controlled study in boys and postmenarchal girls, 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 x ULN were observed more frequently in rosuvastatin compared with placebo-treated children. Four of 130 (3%) children treated with rosuvastatin (2 treated with 10 mg and 2 treated with 20 mg) had increased CK >10 x ULN, compared to 0 of 46 children on placebo.

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.

Presentations and Registration Numbers:
DXM-ROSUVASTATIN FILM COATED TABLET 10 MG:
Box, 3 strips x 10 film coated tablets; MAL25036157AZ
DXM-ROSUVASTATIN FILM COATED TABLET 20 MG:
Box, 3 strips x 10 film coated tablets; MAL25036158AZ

ON MEDICAL PRESCRIPTION ONLY.

STORE AT TEMPERATURES BELOW 30°C.
STORE IN THE ORIGINAL PACKAGE.

KEEP MEDICINES OUT OF REACH OF CHILDREN.

Manufactured by
PT Dexa Medica (Plant) Palembang
Jl. Jenderal Bambang Utoyo No. 138, Kel. 5 Ilir, Kec. Ilir Timur Ii,
Kota Palembang, Sumatera Selatan, Indonesia

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