xxxxxxxx-5343

ROSUVASTATIN CALCIUM

TORUS-10
TORUS-20
10 mg Film-Coated Tablet
20 mg Film-Coated Tablet
Anti-hyperlipidemia

FORMULATION
Each film-coated tablet contains:
Rosuvastatin Calcium equivalent to
Rosuvastatin .....10 mg / 20 mg
PRODUCT DESCRIPTION
Rosuvastatin Calcium (Torus-10) 10 mg Film-Coated Tablet is a pink colored, round, biconvex, film coated tablet with breakline on one side and plain on other side.
Rosuvastatin Calcium (Torus-20) 20 mg Film-Coated Tablet is a pink colored, round, biconvex, beveled edged film coated tablet with breakline on one side and plain surface on other side.
CLINICAL PHARMACOLOGY
Pharmacodynamics:
Rosuvastatin is a 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitor indicated for the treatment of hyperlipidemia. Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase. HMG-CoA reductase is a rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering. It differs structurally from other statins, containing a polar methane sulphonamide group which confers relative hydrophilicity period. The relative hydrophilicity of rosuvastatin imparts greater selectivity for uptake into hepatic versus nonhepatic cells. Rosuvastatin 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. In preclinical studies, the potency of rosuvastatin has been found to be greater than that of other statins (i.e. atorvastatin, simvastatin, pravastatin, lovastatin, cerivastatin, and fluvastatin). 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. It also lowers the LDL-C/ HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.
Pharmacokinetics
Rosuvastatin is incompletely absorbed from the gastrointestinal tract, with a bioavailability of about 20%. Peak plasma concentrations are achieved about 5 hours after an oral dose. It is taken up extensively by the liver, its primary site of action, and undergoes limited metabolism, mainly by the cytochrome P450 isoenzyme CYP2C9. It is about 90% bound to plasma proteins. The plasma elimination half-life of rosuvastatin is about 19 hours. Approximately 90% of an oral dose of rosuvastatin is excreted in the feces, including absorbed and non-absorbed drug, and the remainder is excreted in the urine; about 5% of a dose is excreted unchanged in urine.
INDICATIONS
Adjunctive therapy to diet to reduce elevated Total-C, LDL-C, ApoB, non HDL-C, and triglycerides and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia. Lipidaltering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and nonpharmacological interventions alone has been inadequate.
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 m g/dL and there is a positive family history of premature cardiovascular disease (CVD) or two or more other CVD risk factors.
Adjunctive therapy to diet for the treatment of adult patients with hypertriglyceridemia.
Adjunct to diet for the treatment of patients with primary dysbetalipoproteinemia (Type III Hyperlipoproteinemia).
Adjunctive therapy to other lipid-lowering treatments (e.g., LDL apheresis) or alone if such treatments are unavailable to reduce LDL-C, Total-C, and ApoB in adult patients with homozygous familial hypercholesterolemia.
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.
In individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease based on age ≥ 50 years old in men and ≥ 60 years old in women ,hsCRP ≥2mg/L, and the presence of at least one additional cardiovascular disease risk factor such as hypertension , low HDL-C ,smoking, or a family history of premature coronary heart disease, Rosuvastatin is indicated to:
- Reduce the risk of stroke
- Reduce the risk of myocardial infarction
- Reduce the risk of arterial revascularization procedures

DOSAGE AND ADMINISTRATION:
Before treatment initiation the patient should be placed on a standard cholesterol-lowering diet that should continue during treatment. The dose should be individualized according to the goal of therapy and patient response, using current consensus guidelines.
Rosuvastatin may be given at any time of day, with or without food.
Treatment of hypercholesterolemia
The recommended start dose is 5 or 10 mg orally once daily in both statin naive and patients switched from another HMG CoA reductase inhibitor. The choice of start dose should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions. A dose adjustment to the next dose level can be made after 4 weeks, if necessary. In light of the increased reporting rate of adverse reactions with the 40 mg dose compared to lower doses, a final titration to the maximum dose of 40 mg should only be considered in 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 in whom routine follow-up will be performed. Specialist supervision is recommended when the 40 mg dose is initiated.
Prevention of cardiovascular events
In the cardiovascular events risk reduction study, the dose used was 20 mg daily.
Pediatric population
Pediatric use should only be carried out by specialists.
Children and adolescents 10 to 17 years of age (boys Tanner Stage II and above, and girls who are at least 1 year post-menarche)
In children and adolescents with heterozygous familial hypercholesterolemia the usual start dose is 5 mg daily. The usual dose range is 5-20 mg orally once daily. Titration should be conducted according to the individual response and tolerability in pediatric patients, as recommended by the pediatric treatment recommendations. Children and adolescents should be placed on standard cholesterol-lowering diet before rosuvastatin treatment initiation; this diet should be continued during rosuvastatin treatment. Safety and efficacy of doses greater than 20 mg have not been studied in this population.
The 40 mg tablet is not suitable for use in pediatric patients.
Children younger than 10 years
Experience in children younger than 10 years is limited to a small number of children (aged between 8 and 10 years) with homozygous familial hypercholesterolemia. Therefore, Rosuvastatin is not recommended for use in children younger than 10 years.
Use in the elderly
A start dose of 5 mg is recommended in patients >70 years. No other dose adjustment is necessary in relation to age.
Dosage in patients with renal insufficiency
No dose adjustment is necessary in patients with mild to moderate renal impairment. The recommended start dose is 5 mg in patients with moderate renal impairment (creatinine clearance of <60 ml/min). The 40 mg dose is contraindicated in patients with moderate renal impairment. The use of Rosuvastatin in patients with severe renal impairment is contraindicated for all doses.
Dosage in patients with hepatic impairment
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 is contraindicated in patients with active liver disease.
Race
Increased systemic exposure has been seen in Asian subjects. The recommended start dose is 5 mg for patients of Asian ancestry. The 40 mg dose is contraindicated in these patients.
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 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. The 40 mg dose is contraindicated in some of these patients.
Concomitant therapy
Rosuvastatin is a substrate of various transporter proteins (e.g. OATPIBI 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.
CONTRAINDICATIONS:
Rosuvastatin is contraindicated:
- in patients with hypersensitivit y 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 3 x the upper limit of normal (ULN).
- in patients with severe renal impairment (creatinine clearance <30 m l/min).
- in patients with myopathy.
- in patients receiving concomitant ciclosporin.
- during pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.

The 40 mg dose is contraindicated in patients with pre-disposing factors 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

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 it was transient or intermittent in most cases. Proteinuria has not been shown to be predictive of acute or progressive renal disease. 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
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 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 (>5xULN) a confirmatory test should be carried out within 5-7 days. If the repeat test confirms a base line 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) treatment should not be started.
Whilst on Treatment
Patients should be asked to report inexplicable muscle pain, weakness or cramp s 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 ≤5x ULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing 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 necrotising myopathy (IMNM) during or after treatment with statins, including rosuvastatin. IMNM is clinically characterised by proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.
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 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 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 hypercholesterolemia 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.
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, 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 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/m2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.
Pediatric population
The evaluation of linear growth (height), weight, BMI (body mass index) , and secondary characteristics of sexual maturation by Tanner staging in pediatric patients 10 to 17 years of age taking rosuvastatin is limited to a one-year period. After 52 weeks of study treatment, no effect on growth, weight, BMI or sexual maturation was detected. The clinical trial experience in children and adolescent patients is limited and the long-term effects of rosuvastatin (> 1 year) on puberty are unknown.
Drug Interactions:
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 (see Table 1). Rosuvastatin is contraindicated in patients receiving concomitant ciclosporin. 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 (see Table 1). For instance, in a pharmacokinetic study, 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 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.
Based on data from specific interaction studies no pharmacokinetic relevant interaction with fenofibrate is expected, however a pharmacodynamic interaction may occur. Gemfibrozil , fenofibrate, other fibrates and lipid lowering doses (> or equal to 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.
Ezetimibe: Concomitant use of 10 mg Rosuvastatin and 10 mg ezetimibe resulted in a 1.2 fold increase in AUC of rosuvastatin in hypercholesterolemic subjects (Table 1). 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 aluminum 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.
Erythromycin: Concomitant use of Rosuvastatin and erythromycin resulted in a 20% decrease in AUC 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 1): 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 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 ritonavir/atazanavir (3.1-fold increase).

Table 1 Effect of co-administered medicinal products on rosuvastatin exposure (AUC; in order of decreasing magnitude) from published clinical trials

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 m g/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	20 mg, single dose	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 m g/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-fo1d ↑
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 mg TID, 5 day s	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 "↓".
**several interaction studies have been performed at different Rosu vastatin dosages , the table shows the most significant ratio.
OD = once daily; BID= twice daily; TID= three times daily; QID = four times daily

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. As with other statins, muscle related events, including rhabdomyolysis, have been reported in post marketing experience with rosuvastatin and fusidic acid given concurrently.
Therefore, the combination rosuvastatin and fusidic acid is not recommended. If possible, temporary suspension of rosuvastatin treatment is recommended. If unavoidable, patients should be closely monitored.
Pediatric population: Interaction studies have only been performed in adults . The extent of interactions in the pediatric population is not known.
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 fetus, 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.
Adverse Effects
Based on data from clinical studies and extensive post-marketing experience, the following table 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 convention: Common (≥1/100 to <1110); Uncommon (≥1/1,000 to<1/100); Rare (≥1/10,000 to <1/1000); Very rare (<1/10,000) ; Not known (cannot be estimated from the available data).
Table 2. Adverse reactions based on data from clinical studies and post marketing experience

System organ class	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders			Thrombocytopenia		
Immune system disorders			Hypersensitivity reactions including angioedema		
Endocrine disorders	Diabetes mellitus[1]				
Psychiatric disorders					Depression
Nervous system disorders	Headache Dizziness			Polyneuropathy Memory loss	Peripheral neuropathy Sleep disturbances (including insomnia and nightmares)
Respiratory, thoracic and mediastinal disorders					Cough Dyspnea
Gastro-intestinal disorders	Constipation Nausea Abdominal pam		Pancreatitis		Diarrhea
Hepatobiliary disorders			Increased hepatic transaminases	Jaundice Hepatitis	
Skin and subcutaneous tissue disorders		Pruritis Rash Urticaria			Stevens- Johnson syndrome
Musculo -skeletal and connective tissue disorders	Myalgia		Myopathy (including myositis) Rhabdomyolysis	Arthralgia	Tendon disorders, sometimes complicated by rupture Immune-mediated necrotising myopathy
Renal and urinary disorders				Hematuria	
Reproductive system and breast disorders				Gynecomastia	
General disorders and administration site conditions	Asthenia				Edema

[1]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).

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.
Hematuria 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 (>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; 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.
The reporting rate for rhabdomyolysis, serious renal events and serious hepatic events (consisting mainly of increased hepatic transaminases) is higher at the 40 mg dose.
Pediatric population: Creatine kinase elevations > 10xULN and muscle symptoms following exercise or increased physical activity were observed more frequently in a 52-week clinical trial of children and adolescents compared to adults. In other respects, the safety profile of rosuvastatin was similar in children and adolescents compared to adults.
"For suspected adverse drug reaction, report to FDA: www.fda.gov.ph or to TORRENT: www.torrentpharma.com".
Patient to seek medical attention immediately at the first sign of any adverse drug reaction shall appear.
TREATMENT OF ADVERSE EFFECTS
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.
CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
STORAGE
Store at temperatures not exceeding 30°C. Protect from light and moisture.
AVAILABILITY
Rosuvastatin Calcium (Torus-10) 10 mg Film-Coated Tablet - Alu-Alu Blister pack of 10's (Box of 30's and 100's) – DRP-6581
Rosuvastatin Calcium (Torus-20) 20 mg Film-Coated Tablet - Alu-Alu Blister pack of 10's (Box of 30's and 100's) – DRP-6582
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torrent PHARMA

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TORRENT PHARMACEUTICALS LTD.
Indrad-382 721,Tal: Kadi, City: Indrad,
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TORRENT PHARMA PHILIPPINES INC.
Units 3 & 4, 34th Floor, Zuellig Building
Makati Avenue Corner Paseo de Roxas
Makati City, PHILIPPINES

PRODUCT NAME	:	Torus	**COUNTRY :** Philippines	**LOCATION :** Chhatral	**REMARK :**	
ITEM / PACK	:	Insert	**NO. OF COLORS:** 1	**SUBSTRATE :**		
DESIGN STYLE	:	Front-Back	**PANTONE SHADE NOS.:**			
CODE	:	xxxxxxxx-5343	■ Black	**Activities**	**Department**	**Signature**	**Date**
DIMENSIONS (MM)	:	150 x 530		Prepared By	**Pkg.Dev**		
ART WORK SIZE	:	S/S		Reviewed By	**Pkg.Dev**		
DATE	:	22-06-2016		Approved By	**Quality**		
	:						