Bosch

For Medical Professional only

Rova Tablets

(Rosuvastatin)

روواٹیبلیٹس

(روزوواسٹیٹن)

DESCRIPTION:
ROVA (rosuvastatin calcium) is a synthetic lipid-lowering agent for oral administration. The chemical name for rosuvastatin calcium is bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt. Rosuvastatin calcium is a white amorphous powder with empirical formula $(C_{22}H_{27}FN_3O_6S)_2Ca$ and the molecular weight is 1001.14.

COMPOSITION:
Each Rova 5mg film coated tablet contains :
Rosuvastatin..... 5mg as Rosuvastatin Calcium U.S.P.
(Product Specs.: U.S.P.)

Each Rova 10mg film coated tablet contains :
Rosuvastatin..... 10mg as Rosuvastatin Calcium U.S.P.
(Product Specs.: U.S.P.)

Each Rova 20mg film coated tablet contains :
Rosuvastatin..... 20mg as Rosuvastatin Calcium U.S.P.
(Product Specs.: U.S.P.)

CLINICAL PHARMACOLOGY:
Pharmacodynamic Properties:
Pharmacotherapeutic group: Lipid modifying agents, plain, HMG-CoA reductase inhibitors, ATC code: C10A A07.

Mechanism of Action:
Rosuvastatin is a selective 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. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering.

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.

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. Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

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

Distribution:
Rosuvastatin is taken up extensively by the liver which is the primary site of cholesterol synthesis and LDL-C clearance. The volume of distribution of rosuvastatin is approximately 134 L. Approximately 90% of rosuvastatin is bound to plasma proteins, mainly to albumin.
Metabolism:
Rosuvastatin undergoes limited metabolism (approximately 10%). Rosuvastatin is a poor substrate for cytochrome P450-based metabolism. CYP2C9 was the principal isoenzyme involved, with 2C19, 3A4 and 2D6 involved to a lesser extent. The main metabolites identified are the N-desmethyl and lactone metabolites. The N-desmethyl metabolite is approximately 50% less active than rosuvastatin whereas the lactone form is considered clinically inactive. Rosuvastatin accounts for greater than 90% of the circulating HMG-CoA reductase inhibitor activity.

Elimination:
Approximately 90% of the rosuvastatin dose is excreted unchanged in the faeces and the remaining part is excreted in urine. Approximately 5% is excreted unchanged in urine. The plasma elimination half-life is approximately 19 hours. The elimination half-life does not increase at higher doses. The geometric mean plasma clearance is approximately 50 litres/hour (coefficient of variation 21.7%). As with other HMG-CoA reductase inhibitors, the hepatic uptake of rosuvastatin involves the membrane transporter OATP-C. This transporter is important in the hepatic elimination of rosuvastatin.

SPECIFIC POPULATIONS
Renal Impairment
Mild to moderate renal impairment (CLcr ≥30 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 (CLcr <30 mL/min/1.73 m^2) not receiving hemodialysis compared with healthy patients (CLcr >80 mL/min/1.73 m^2).

Steady-state plasma concentrations of rosuvastatin in patients on chronic hemodialysis were approximately 50% greater compared with normal renal function.

Hepatic Impairment
In patients with chronic alcohol liver disease, plasma concentrations of rosuvastatin were modestly increased. In patients with Child-Pugh A disease, Cmax and AUC

were increased by 60% and 5%, respectively, as compared with patients with normal liver function. In patients with Child-Pugh B disease, Cmax and AUC were increased 100% and 21%, respectively, compared with patients with normal liver function.

Pediatrics:
Patients with heterozygous familial hypercholesterolemia 10 to 17 years of age and 8 to 17 years of age, respectively, rosuvastatin exposure appeared comparable to or lower than rosuvastatin exposure in adult patients.

Elderly:
There were no differences in plasma concentrations of rosuvastatin between the nonelderly and elderly populations (age ≥65 years).

THERAPEUTIC INDICATIONS:
Treatment of hypercholesterolaemia
Adults, adolescents and children aged 6 years or older with primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

Prevention of Cardiovascular Events
Prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors.

DOSAGE AND ADMINISTRATION:
Adults:
The dose range for Rosuvastatin in adults is 5 to 40 mg orally once daily. The usual starting dose is 10 to 20 mg once daily. The usual starting dose in adult patients with homozygous familial hypercholesterolemia is 20 mg once daily. The maximum Rosuvastatin dose of 40 mg should be used only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose. Rosuvastatin can be administered as a single dose at any time of day, with or without food. The tablet should be swallowed whole.

Before treatment initiation the patient should be placed on a standard cholesterol-lowering diet that should continue during treatment. When initiating Rosuvastatin therapy or switching from another HMG-CoA reductase inhibitor therapy, the appropriate Rosuvastatin starting dose should first be utilized, and only then titrated according to the patient's response and individualized goal of therapy. After initiation or upon titration of Rosuvastatin, lipid levels should be analyzed within 2 to 4 weeks and the dosage adjusted accordingly.

In Asian patients, consider initiation of Rosuvastatin therapy with 5 mg once daily due to increased rosuvastatin plasma concentrations. The increased systemic exposure should be taken into consideration when treating Asian patients not adequately controlled at doses up to 20 mg/day.

Pediatric Dosing
In heterozygous familial hypercholesterolemia, the recommended dose range is 5 to 10 mg orally once daily in patients 8 to less than 10 years of age, and 5 to 20 mg orally once daily in patients 10 to 17 years of age. In homozygous familial hypercholesterolemia, the recommended dose is 20 mg orally once daily in patients 7 to 17 years of age. Rosuvastatin is not recommended for use in children younger than 6 years.

Elderly:
A start dose of 5 mg is recommended in patients >70 years. No other dose adjustment is necessary in relation to age.

Patients with Renal Impairment:
For patients with severe renal impairment (CLcr <30 mL/min/1.73 m^2) not on hemodialysis, dosing of Rosuvastatin should be started at 5 mg once daily and not exceed 10 mg once daily. The use of Rosuvastatin in patients with severe renal impairment is contraindicated for all doses.

CONTRAINDICATIONS:
Rosuvastatin is contraindicated:
- In patients with hypersensitivity to the active substance 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 mL/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:
Lactose:
Rosuvastatin contains lactose. Possibility of untoward reaction for patient with celiac disease relating to the use of such excipients. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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.

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.

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

Before Treatment
Rosuvastatin, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis.
Such factors include: Renal impairment, hypothyroidism, personal or family history of hereditary muscular disorders, previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate, alcohol abuse, age >70 years, situations where an increase in plasma levels may occur, and concomitant use of fibrates.

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

During Treatment
Patients should be asked to report inexplicable muscle pain, weakness or cramps immediately, particularly if associated with malaise or fever. CK levels should be measured in these patients. Therapy should be discontinued if CK levels are markedly elevated (>5xULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤5x ULN). There have been very rare reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with statins, including rosuvastatin. IMNM is clinically characterized by proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment. The combination of Rosuvastatin and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of Rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of such combinations. Rosuvastatin 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 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.

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.

In patients with secondary hypercholesterolaemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with Rosuvastatin. The reporting rate for serious hepatic events in post-marketing use is higher at the 40 mg dose.

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. If it is suspected that 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.

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions including Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with rosuvastatin. At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of this reaction appears, Rosuvastatin should be discontinued immediately, and an alternative treatment should be considered.

If the patient has developed a serious reaction such as SJS or DRESS with the use of Rosuvastatin, treatment with rosuvastatin must not be restarted in this patient at any time.

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

Ciclosporin:
Rosuvastatin 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. The concomitant use of Rosuvastatin and some protease inhibitor combinations may be considered after careful consideration of Rosuvastatin dose adjustments based on the expected increase in rosuvastatin exposure.

Gemfibrozil and other lipid-lowering products:
Concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin Cmax and AUC. 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 hypercholesterolaemic patients.

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.

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

Cytochrome P450 enzymes:
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).

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.

Fusidic Acid:
The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction is yet unknown. There have been reports of rhabdomyolysis 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.

ADVERSE EFFECTS:
Common:
Diabetes mellitus, Headache, Dizziness, Constipation, Nausea, Abdominal pain, Myalgia, Asthenia

Uncommon:
Pruritus, Rash, Urticaria

Rare:
Thrombocytopenia, Hypersensitivity reactions including angioedema, Pancreatitis, Increased hepatic transaminases, Myopathy (including myositis), Rhabdomyolysis, Lupus-like syndrome, Muscle rupture

Very Rare:
Polyneuropathy, Memory loss, Jaundice, Hepatitis, Arthralgia, Haematuria, Gynaecomastia

Not Known:
Depression, Peripheral neuropathy, Sleep disturbances (including insomnia and nightmares), Cough, Dyspnoea, Diarrhoea, Stevens-Johnson Syndrome, Drug reaction with eosinophilia and systemic symptoms (DRESS), Tendon disorders sometimes, complicated by rupture, Immune-mediated necrotising myopathy, Oedema

USE IN PREGNANCY AND LACTATION:
Pregnancy:
Rosuvastatin is contraindicated in pregnancy and lactation. Women of child bearing potential should use appropriate contraceptive measures. If a patient becomes pregnant during use of this product, treatment should be discontinued immediately.

Lactation:
Rosuvastatin use is contraindicated during breastfeeding. Because of the potential for serious adverse reactions in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with Rosuvastatin.

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.

INSTRUCTIONS:
Protect from heat, sunlight and moisture, store below 30°C.
Keep out of the reach of children
Patients and healthcare professionals can also report suspected adverse drug reaction at ade@bosch-pharma.com.
To be sold on prescription of a registered medical practitioner only.
"Product contains lactose"

PRESENTATION:
Rova 5 mg tablets : Pack of 10 tablets in Cold Form & Cold Seal (Alu Alu) Blister packing.
Rova 10 mg tablets : Pack of 10 tablets in Cold Form & Cold Seal (Alu Alu) Blister packing.
Rova 20 mg tablets : Pack of 10 tablets in Cold Form & Cold Seal (Alu Alu) Blister packing.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: دھوپ، گرمی اور نمی سے محفوظ ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

بچوں کی پہنچ سے دور رکھیں۔

صرف مستند ڈاکٹر کے نسخے پر فروخت کے لئے۔

Manufactured by:
Bosch Pharmaceuticals (Pvt) Ltd.
221-223, Sector 23, Korangi Industrial Area,
Karachi - Pakistan

ISO 9001:2015 Certified Company