ROVIN Tablets
(Rosuvastatin) USP

5mg
10mg
20mg

DESCRIPTION:
ROVIN (Rosuvastatin as calcium) USP is a synthetic oral lipid-lowering agent. The molecular formula for Rosuvastatin Calcium is $Ca(C_{22}H_{27}FN_3O_6S)_2$

COMPOSITION:
ROVIN (Rosuvastatin as calcium) USP is available for oral administration as:
ROVIN Tablet 5mg:
Each film-coated tablet contains:
Rosuvastatin as calcium (USP).....5mg

ROVIN Tablet 10mg:
Each film-coated tablet contains:
Rosuvastatin Calcium (USP).....10mg

ROVIN Tablet 20mg:
Each film-coated tablet contains:
Rosuvastatin Calcium (USP).....20mg

Product compiles with USP Dissolution Test 3.

CLINICAL PHARMACOLOGY:
Mechanism of Action:
Rosuvastatin Calcium is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methyl glutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of Rosuvastatin Calcium is the liver, the target organ for cholesterol lowering. Rosuvastatin increase the numbers 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.

PHARMACOKINETICS:
Absorption:
Rosuvastatin Calcium is administered orally following which the active moiety, is rapidly absorbed, reaching peak plasma concentration 3 to 5 hours after dosing.
Both peak concentration (Cmax) and area under the plasma concentration-time curve (AUC) increase in proportion to Rosuvastatin Calcium dose. The absolute bioavailability of Rosuvastatin Calcium is approximately 20% and there is no accumulation on repeated dosing. Rosuvastatin Calcium may be given with or without food. Administration in the morning or evening did not affect the rate and extent of absorption nor the ability of Rosuvastatin Calcium to reduce LDL-C.

Distribution:
Rosuvastatin Calcium undergoes first pass metabolism in the liver, which is the primary site of cholesterol synthesis and LDL-C clearance. The mean volume of distribution at steady state of Rosuvastatin Calcium is approximately 134 litres. Rosuvastatin Calcium is approximately 90% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.

Metabolism:
Rosuvastatin Calcium is not extensively metabolised with approximately 10% of a radiolabeled dose recovered as metabolite. The major metabolite is N-desmethyl Rosuvastatin Calcium, which is formed principally by cytochrome P450 2C9, and in vitro studies has demonstrated to have approximately one-half the HMG-CoA reductase inhibitory activity of Rosuvastatin Calcium. The parent compound accounts for greater than 87% of the circulating active HMG-CoA reductase inhibitory activity.

Excretion:
Following an oral dose, Rosuvastatin Calcium and its metabolites are primarily excreted in the faeces (90%) with the remainder being excreted in the urine. Fecal recovery represents absorbed drug metabolites in the bile and unabsorbed drug. The elimination half-life (t½) of Rosuvastatin Calcium is approximately 19 hours and does not increase with increasing doses.

THERAPEUTIC INDICATIONS:
Rosuvastatin Calcium is indicated for the treatment of:
Hypercholesterolemia:
Rosuvastatin Calcium is indicated as an adjunct to diet for the reduction of elevated total cholesterol
(Total-C), LDL-C, ApoB, the Total-C/HDL-C ratio and triglycerides (TG) and for increasing HDL-C; in hyperlipidemic and dyslipidemic conditions, when response to diet and exercise alone has been inadequate including:

- Primary hypercholesterolemia (Type IIa including heterozygous familial hypercholesterolemia and severe non-familial hypercholesterolemia)
- Combined (mixed) dyslipidemia (Type IIb)
- Homozygous familial hypercholesterolemia
- Hypertriglyceridemia
- Hyperlipoproteinemia Type III
- Slow progression of Atherosclerosis

Prevention of Major Cardiovascular Events:
In adult patients without documented history of cardiovascular or cerebrovascular events, but with at least two conventional risk factors for cardiovascular disease. Rosuvastatin Calcium is indicated to:

- Reduce the risk of nonfatal myocardial infarction
- Reduce the risk of nonfatal stroke
- Reduce the risk of coronary artery revascularization

Pediatric Patients 7 to 17 years of age with Heterozygous Familal Hypercholesterolemia (HeFH)
Rosuvastatin Calcium is indicated as an adjunct to diet for the reduction of elevated Total-C, LDL-C and ApoB levels in adolescent boys and girls, who are at least one year postmenarche, 10-17 years of age with heterozygous familial hypercholesterolemia when response to diet alone has been inadequate.

RECOMMENDED DOSAGE
Hypercholesterolemia
The dose range of Rosuvastatin Calcium is 5 to 40mg orally once a day. The recommended starting dose of Rosuvastatin Calcium in most patients is 10mg orally once daily. The majority of patients are controlled at the 10mg dose. If necessary, dose adjustment can be made at 2-4 week intervals. The maximum response is usually achieved within 2-4 weeks and is maintained during chronic therapy.
Initiation of therapy with Rosuvastatin Calcium 5mg once daily may be considered for patients requiring less aggressive LDL-C reductions or who have predisposing factors for myopathy.
Patients who are switched to Rosuvastatin Calcium from treatment with another HMG-CoA reductase inhibitor should be started on 10mg even if they were on a high dose of the previous HMG-CoA reductase inhibitor. A switch dose of 20mg may be considered for patients with severe hypercholesterolemia.
For patients with severe hypercholesterolemia (including those with familial hypercholesterolemia), a 20mg start dose may be considered. These patients should be carefully followed.
A dose of 40mg once daily should only be used in patients with severe hypercholesterolemia who do not achieve the desired effect on 20mg and have no predisposing factors for myopathy/rhabdomyolysis.
The dosage of Rosuvastatin Calcium should be individualized according to baseline LDL-C, total C/HDL-C ratio and/or TG levels to achieve the recommended desired lipid values at the lowest possible dose.

Prevention of Major Cardiovascular Events
A dose of 20mg once daily has been found to reduce the risk of major cardiovascular events.

DOSING CONSIDERATIONS IN SPECIAL POPULATIONS:
Patients with Hepatic Impairment:
The usual dose range applies in patients with mild to moderate hepatic impairment. Increased systemic exposure has been observed in patients with severe hepatic impairment and, therefore, in these patients the dose of Rosuvastatin Calcium should not exceed 20mg once daily.

Patients with Renal Impairment:
The usual dose range applies in patients with mild to moderate renal impairment. Increased systemic exposure to Rosuvastatin Calcium has been observed in patients with severe renal impairment.
For patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m^2) the starting dose of Rosuvastatin Calcium should be 5mg and should not exceed 10 mg once daily.

Race:
The initial dose of Rosuvastatin Calcium in Asian patients, should be 5mg once daily. The potential for increase in systemic exposure must be considered when making treatment decisions. The maximum dose should not exceed Rosuvastatin Calcium 20mg once daily.

Pediatrics (10 – 17 years of age):
In pediatric patients with heterozygous familial hypercholesterolemia the recommended starting dose of Rosuvastatin Calcium is 5mg taken orally once daily. The Rosuvastatin Calcium dose should be individualized according to baseline LDL-C levels and the recommended goal of therapy. The maximum daily dose in this patient population is 10 mg.

Elderly:
No dose adjustment is necessary.

Concomitant Therapy:
Rosuvastatin Calcium is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when Rosuvastatin Calcium is administered concomitantly with certain medicines that may increase the plasma concentration of Rosuvastatin Calcium due to interactions with these transporter proteins.
Whenever possible, alternative medications should be considered, and if necessary, consider temporarily discontinuing Rosuvastatin Calcium therapy. In situations where coadministration of these medicines with Rosuvastatin Calcium is unavoidable, the benefit and the risk of concurrent treatment and Rosuvastatin Calcium dosing adjustments should be carefully considered.

SPECIFIC POPULATIONS
Pregnancy:
Safety in pregnant women not established; no known benefits with use during pregnancy. Discontinue immediately if pregnancy is known or suspected.

Lactation:
Distributed into human milk; effects on breast-fed infants or milk production not known. Use is contraindicated in nursing women; women who require Rosuvastatin Calcium therapy should not breast-feed their infants.

Pediatric Use:
Safety and efficacy is not established in children <8 years of age.
Safety and efficacy in pediatric patients 8–17 years of age with heterozygous familial hypercholesterolemia generally similar to those observed in the adult population.

Geriatric Use:
No substantial differences in safety and efficacy relative to younger adults; however, increased sensitivity cannot be ruled out.
Use with caution, since age ≥65 is a predisposing risk factor for myopathy. In patients >75 years of age, consider benefits, adverse effects, drug interactions, and patient preferences before initiating statin therapy.

CONTRAINDICATIONS:
Rosuvastatin Calcium is contraindicated:

- In patients who are hypersensitive to any component of this medication.
- In patients with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal.
- In pregnant and nursing women
- Cholesterol and other products of cholesterol biosynthesis are

essential components for fetal development (including synthesis of steroids and cell membranes). Rosuvastatin Calcium should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the possible harm.

If the patient becomes pregnant while taking Rosuvastatin Calcium, the drug should be discontinued immediately and the patient apprised of the potential harm to the fetus. Atherosclerosis being a chronic process, discontinuation of lipid metabolism regulating drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia.

- In patients using concomitant cyclosporine
- In patients using concomitant sofosbuvir/velpatasvir/voxilaprevir
- Rosuvastatin Calcium dose more than 40 mg is contraindicated in:
- Asian patients
- Patients with pre-disposing factors for myopathy/rhabdomyolysis such as:
- Personal or family history of hereditary muscular disorders
- Previous history of muscle toxicity with another 3-Hydroxyl-3
- Methylglutaryl- Coenzyme A (HMG-CoA) reductase inhibitor
- Concomitant use of a fibrate or niacin
- Severe hepatic impairment
- Severe renal impairment (CrCl < 30 mL/min/1.73 m^2)
- Hypothyroidism
- Alcohol abuse
- Situations where an increase in Rosuvastatin Calcium plasma levels may occur

ADVERSE REACTIONS

Rosuvastatin Calcium is generally well tolerated. Adverse reactions have usually been mild and transient.

Common:

Headache, dizziness, constipation, nausea, abdominal pain, myalgia, asthenia and diabetic mellitus.

Uncommon:

Pruritus, rash and urticaria.

Rare:

Thrombocytopenia, Hypersensitivity reactions including angioedema, pancreatitis. Increased hepatic transaminases, myopathy, rhabdomyolysis, Lupus like syndrome and muscle rupture.

WARNINGS AND PRECAUTIONS:

- Before instituting therapy with Rosuvastatin Calcium an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in overweight patients and to treat other underlying medical problems and associated cardiovascular risk factors. The patient should be advised to inform subsequent physicians of theprior use of Rosuvastatin Calcium or any other lipid-lowering agent.

- **Hepatic Impairment**

Rosuvastatin Calcium is contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal.

Rosuvastatin Calcium should be discontinued or the dose reduced if the level of transaminases is greater than 3 times the upper limit of normal. Rosuvastatin Calcium, as well as other HMG-CoA reductase inhibitors should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease.

As with other HMG-CoA reductase inhibitors, a dose-related increase in transaminases has been observed in a small number of patients taking Rosuvastatin Calcium (< 0.5%); the majority of cases were mild, asymptomatic and transient. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with Rosuvastatin Calcium, promptly interrupt therapy. In subjects with varying degrees of hepatic impairment there was no evidence of increased exposure to Rosuvastatin Calcium in subjects with Child-Pugh scores of 7 or below. However, two subjects with Child-Pugh scores of 8 and 9 showed an increase in systemic exposure of at least 2-fold compared to subjects with lower Child-Pugh scores. There is no experience in subjects with Child-Pugh scores above 9.

- **Renal Impairment**

Patients with severe renal impairment (CrCl < 30 mL/min/1.73m2) had a 3-fold increase in plasma concentration of Rosuvastatin Calcium. In patients with varying degrees of renal impairment, mild to moderate renal disease had little influence on plasma concentrations of Rosuvastatin Calcium. A dose reduction may be considered for patients with unexplained persistent proteinuria during routine testing.

- **Muscle Effects**

Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in Rosuvastatin Calcium-treated patients with all doses. 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 excludedand caution should be exercised with their combined use.

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.

Rosuvastatin Calcium, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- Personal or family history of hereditary muscular disorders
- Previous history of muscle toxicity with another HMG-CoA reductase inhibitor
- Concomitant use of a fibrate or niacin
- Hypothyroidism
- Alcohol abuse
- Excessive physical exercise
- Age > 70 years
- Renal impairment
- Hepatic impairment
- Diabetes with hepatic fatty change
- Surgery and trauma
- Frailty
- Situations where an increase in plasma levels of Rosuvastatin Calcium may occur.

Rosuvastatin Calcium therapy should be temporarily withheld or discontinued in any patient with an acute serious condition suggestive of myopathy or predisposing to the development of rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic endocrine and electrolyte disorders, or uncontrolled seizures).

DRUG INTEERACTIONS:

Cytochrome P450 Inhibitors:

Rosuvastatin Calcium has no clinically significant cytochrome P450 interactions. Consequently, there is little potential for drug-drug interactions upon coadministration with agents that are metabolised by cytochrome P450. Rosuvastatin Calcium clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent.

Cyclosporine:

The concomitant use of Rosuvastatin Calcium and immunosuppressant cyclosporine is contraindicated

Protease Inhibitors:

Coadministration of Rosuvastatin Calcium with certain protease inhibitors may increase the Rosuvastatin Calcium exposure, (AUC) up to 7-fold. Rosuvastatin Calcium use should be stopped or dose adjustment should be done depending on the level of effect on Rosuvastatin Calcium exposure.

Transporter Protein Inhibitors:

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

Coumarin Anticoagulants:

In patients taking coumarin, monitoring of INR is recommended at initiation or cessation of therapy with Rosuvastatin Calcium or following dose adjustment. Rosuvastatin Calcium therapy has not been associated with bleeding or changes in INR in patients not taking anticoagulants.

Concomitant Therapy with Other Lipid Metabolism Regulators

Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses of niacin (nicotinic acid) may increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. Therefore, combined drug therapy should be approached with caution.

Antacid:

Simultaneous dosing of Rosuvastatin Calcium with an antacid suspension containing aluminium and magnesium hydroxide resulted in a decrease in Rosuvastatin Calcium plasma concentration by approximately 50%. The antacid should be dosed 2 hours after Rosuvastatin Calcium.

DRUG OVERDOSE:

There is no specific treatment in the event of overdosage. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted as required.

Hemodialysis does not significantly enhance clearance of Rosuvastatin Calcium.

INSTRUCTIONS:

Store at 15-30°C.

Protect from heat light and moisture.

Keep all medicines out of the reach of children.

To be sold on the prescription of a registered medical practitioner only.

HOW SUPPLIED:

ROVIN (Rosuvastatin as Calcium) USP Tablets 5mg: Pack of 10's

ROVIN (Rosuvastatin as Calcium) USP Tablets 10mg: Pack of 10's

ROVIN (Rosuvastatin as Calcium) USP Tablets 20mg: Pack of 10's

روون

گولیاں

(روزوواسٹیٹن کیلشیم) یو ایس پی

خوراک: دوا ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: دوا کو **15-30°** سینٹی گریڈ پر رکھیں۔

گرمی، روشنی اور نمی سے محفوظ رکھیں۔ تمام دوائیں بچوں کی پہنچ سے دُور رکھیں۔

صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by:
STANDPHARM PAKISTAN (PVT) LTD
20 Km Ferozepur Road Lahore, Pakistan.

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