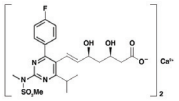
ROSULIP®

(Rosuvastatin)

रोजुलिप

DESCRIPTION:

ROSULIP (Rosuvastatin calcium) is a synthetic lipid-lowering agent for oral administration.The empirical formula for Rosuvastatin calcium is (C22H27FN3O6S)2Ca and the molecular weight is 1001.14. ROSULIP Tablets for oral administration contain 5, 10, or 20 mg of Rosuvastatin.



CLINICAL PHARMACOLOGY:

Mechanism of Action

ROSULIP 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 of cholesterol. In-vivo studies in animals, and in vitro studies in cultured animal and human cells have shown Rosuvastatin to have a high uptake into, and selectivity for, action in the liver, the target organ for cholesterol lowering. In in-vivo and in-vitro studies, Rosuvastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, Rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.

Pharmacodynamics:

ROSULIP dose dependently reduces elevated LDL-cholesterol and reduces total cholesterol and triglycerides and increases HDL-cholesterol. A therapeutic response to Rosuvastatin (ROSULIP) is evident within 1 week of commencing therapy and 90% of maximum response is usually achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that. Individualization of drug dosage should be based on the therapeutic response.

Pharmacokinetics:

Absorption: In clinical pharmacology studies in man, peak plasma concentrations of Rosuvastatin were reached 3 to 5 hours following oral dosing. Both Cmax and AUC increased in approximate proportion to Rosuvastatin (ROSULIP) dose. The absolute bioavailability of Rosuvastatin is approximately 20%.Administration of Rosuvastatin (ROSULIP) with food did not affect the AUC of Rosuvastatin.The AUC of Rosuvastatin does not differ following evening or morning 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.

Elimination: Rosuvastatin is primarily eliminated by excretion in the feces. The elimination half-life of Rosuvastatin is approximately 19 hours.

Metabolism: Rosuvastatin is not extensively metabolized; approximately 10% of a radiolabeled dose is recovered as metabolite. The major metabolite is N-desmethylrosuvastatin, which is formed principally by cytochrome P450 \ 2C9, and in vitro studies have demonstrated that N-desmethylrosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of the parent compound. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by the parent compound.

Excretion: Following oral administration, Rosuvastatin and its metabolites are primarily excreted in the feces (90%). After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route.

INDICATIONS:

Hyperlipidemia and Mixed Dyslipidemia: ROSULIP is indicated as adjunctive therapy to diet to reduce elevated Total-C, LDL-C, ApoB, nonHDL-C, and triglycerides and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia. Lipid-altering 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. Pediatric Patients with Familial Hypercholesterolemia: ROSULIP is indicated as an adjunct to diet to: 1) reduce Total-C, LDL-C and ApoB levels in children and adolescents 8 to 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 along with a positive family history of premature cardiovascular disease (CVD) or two or more other CVD risk factors.

2) reduce LDL-C, Total-C, nonHDL-C and ApoB in children and adolescents 7 to 17 years of age with homozygous familial hypercholesterolemia, either alone or with other lipid-lowering treatments (e.g., LDL apheresis).

Hypertriglyceridemia: ROSULIP is indicated as adjunctive therapy to diet for the treatment of adult patients with hypertriglyceridemia.

Primary Dysbetalipoproteinemia (Type III Hyperlipoproteinemia): ROSULIP is indicated as an adjunct to diet for the treatment of adult patients with primary dysbetalipoproteinemia (Type III Hyperlipoproteinemia). Adult Patients with Homozygous Familial Hypercholesterolemia: ROSULIP is indicated as 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.

Slowing of the Progression of Atherosclerosis: ROSULIP 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. Primary Prevention of Cardiovascular Disease: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 ≥2 mg/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, ROSULIP is indicated to: 1) reduce the risk of stroke 2) reduce the risk of myocardial infarction 3) reduce the risk of arterial revascularization procedures.

Limitations of Use: Rosuvastatin has not been studied in Fredrickson Type I and V dyslipidemias.

DOSAGE & ADMINISTRATION:

General Dosing Information: The dose range for ROSULIP 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 ROSULIP dose of 40 mg should be used only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose.ROSULIP can be administered as a single dose at any time of day, with or without food. The tablet should be swallowed whole. When initiating ROSULIP therapy or switching from another HMG-CoA reductase inhibitor therapy, the appropriate ROSULIP 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 ROSULIP, lipid levels should be analyzed within 2 to 4 weeks and the dosage adjusted accordingly.

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.

Dosing in Patients with Severe Renal Impairment: For patients with severe renal impairment (CLcr<30 mL/min/1.73 m2) not on hemodialysis, dosing of ROSULIP should be started at 5 mg once daily and not exceed 10 mg once daily.

ADVERSE DRUG REACTIONS:

Adverse effects are generally mild and transient. As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to be dose dependent. Some adverse effects seen with this drug are as follow; Myalgia, asthenia, diabetes mellitus, headache, dizziness, constipation, nausea,abdominal pains are common side effect of Rosuvastatin.Hypersensitivity reactions including angioedema, pruritus, rash and urticaria,pancreatitis, myopathy (including myositis) and rhabdomyolysis are rarely seen sideeffect of Rosuvastatin.

CONTRAINDICATIONS:

Hypersensitive to Rosuvastatin or to any of the excipient; Liver disease; Severe renal impairment; Myopathy; Patient receiving concomitant cyclosporine; Pregnancy and lactation; 40 mg dose is contraindicated in the patient with pre disposing factor for myopathy/rhabdomyolysis, pediatrics.

DRUG INTERACTIONS:

- Vitamin K antagonists
- Very rare cases of rhabdomyolysis have been reported with the use of Ezetimibe in combination with HMG-CoA reductase inhibitors. A pharmacodynamic interaction cannotbe excluded and caution should be exercised with their combined use.
- Concomitant use of Rosuvastatin and Gemfibrozil resulted in a 2-fold increase in Rosuvastatin C max 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.
- Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase Rosuvastatin exposure.
- 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.
- 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.
- 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.

SPECIAL PRECAUTIONS:

Patients with rare hereditary problems of galactose intolerance, the Lapp lactasedeficiency or glucose-galactose malabsorption should not take this medicine.Should not be used in any patient with an acute or serious condition suggestive ofmyopathy or predisposing to the development of renal failure secondary torhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic,endocrine and electrolyte disorders; or uncontrolled seizures).Should be used with caution in patients who consume excessive quantities of alcoholand/or have a history of liver disease. It is recommended that liver function tests becarried out prior to, and 3 months following, the initiation of treatment. Rosuvastatinshould be discontinued or the dose reduced if the level of serum transaminases isgreater than 3 times the upper limit of normal.In patients with secondary hypercholesterolemia caused by hypothyroidism or nephroticsyndrome, the underlying disease should be treated prior to initiating therapy with Rosuvastatin.

PRESENTATION:

ROSULIP-5:

- Each film coated tablet contains: Rosuvastatin calcium equivalent to Rosuvastatin 5 mg.
  Packaging: 30 Tablets X 5 Blisters

ROSULIP-10:

- Each film coated tablet contains: Rosuvastatin calcium equivalent to Rosuvastatin 10 mg.
  Packaging: 30 Tablets X 5 Blisters

ROSULIP-20:

- Each film coated tablet contains: Rosuvastatin calcium equivalent to Rosuvastatin 20 mg.
  Packaging: 30 Tablets X 5 Blisters

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