Size : 165x120 mm

Rosuvastatin

Lowas 10

10 mg Film-Coated Tablet
HMG CoA Reductase Inhibitor

℞

FORMULATION:
Each film-coated tablet contains:
Rosuvastatin (as calcium).....10 mg

PRODUCT DESCRIPTION:
Red coloured round, biconvex, film-coated tablets plain on both sides.

CLINICAL PHARMACOLOGY:
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 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 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.

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 dose. The absolute bioavailability of Rosuvastatin is approximately 20%.
Administration of Rosuvastatin 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.
Metabolism: Rosuvastatin is not extensively metabolized; approximately 10% of a radiolabeled 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 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%). The elimination half-life (t1/2) 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.
Race: A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic, and Black or Afro-Caribbean groups. However, pharmacokinetic studies, including one conducted in the US, have demonstrated an approximate 2-fold elevation in median exposure (AUC and Cmax) in Asian subjects when compared with a Caucasian control group.
Gender: There were no differences in plasma concentrations of Rosuvastatin between men and women.
Geriatric: There were no differences in plasma concentrations of Rosuvastatin between the nonelderly and elderly populations (age ≥ 65 years).
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 subjects (CLcr > 80 mL/min/1.73 m^2).
Hemodialysis: Steady-state plasma concentrations of Rosuvastatin in patients on chronic hemodialysis were approximately 50% greater compared with healthy volunteer subjects 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.

INDICATIONS:
It is used to reduce LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol in the management of hyperlipidemia, including primary hypercholesterolemia (type IIa), mixed dyslipidaemia (type IIb), and hypertriglyceridemia (type IV), as well as in patients with homozygous familial hypercholesterolemia. It is also used to reduce the progression of atherosclerosis.

DOSAGE AND ADMINISTRATION:
Initially 5-10 mg once daily increased if necessary at intervals of at least 4 weeks to 20 mg once daily, increased after further 4 weeks to 40 mg daily only in severe hypercholesterolemia with high cardiovascular risk and under specialist supervision.
Or as prescribed by the physician.

CONTRAINDICATIONS:
Known hypersensitivity to the active substance or to any of the excipients.

WARNINGS AND PRECAUTIONS:
Skeletal Muscle Effects: Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including Rosuvastatin. These risks can occur at any dose level, but are increased at the highest dose (40 mg).
Rosuvastatin should be prescribed with caution in patients with predisposing factors for myopathy (e.g., age ≥ 65 years, inadequately treated hypothyroidism, renal impairment).
The risk of myopathy during treatment with Rosuvastatin may be increased with concurrent administration of some other lipid-lowering therapies (fibrates or niacin), gemfibrozil, cyclosporine, lopinavir/ritonavir, or atazanavir/ritonavir. Cases of myopathy, including rhabdomyolysis, have been reported with HMG-CoA reductase inhibitors, including Rosuvastatin, co-administered with colchicine, and caution should be exercised when prescribing Rosuvastatin with colchicine.
Rosuvastatin therapy should be discontinued if markedly elevated creatine kinase levels occur or myopathy is diagnosed or suspected. Rosuvastatin therapy should also be temporarily withheld 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, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures).
There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: 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.
All patients should be advised to promptly report to their physician unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing Rosuvastatin.

Liver Enzyme Abnormalities: It is recommended that liver enzyme tests be performed before the initiation of Rosuvastatin, and if signs or symptoms of liver injury occur.
Increases in serum transaminases [AST(SGOT) or ALT(SGPT)] have been reported with HMG-CoA reductase inhibitors, including Rosuvastatin. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. There were two cases of jaundice, for which a relationship to Rosuvastatin therapy could not be determined, which resolved after discontinuation of therapy. There were no cases of liver failure or irreversible liver disease in these trials.
In a pooled analysis of placebo-controlled trials, increases in serum transaminases to > 3 times the upper limit of normal occurred in 1.1% of patients taking Rosuvastatin versus 0.5% of patients treated with placebo.
There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including Rosuvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with Rosuvastatin, promptly interrupt therapy. If an alternate etiology is not found, do not restart Rosuvastatin.
Rosuvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of chronic liver disease. Active liver disease, which may include unexplained persistent transaminase elevations, is a contraindication to the use of Rosuvastatin.
Concomitant Coumarin Anticoagulants: Caution should be exercised when anticoagulants are given in conjunction with Rosuvastatin because of its potentiation of the effect of coumarin-type anticoagulants in prolonging the prothrombin time/INR. In patients taking coumarin anticoagulants and Rosuvastatin concomitantly, INR should be determined before starting Rosuvastatin and frequently enough during early therapy to ensure that no significant alteration of INR occurs.
Proteinuria and Hematuria: In the Rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among Rosuvastatin treated patients. These findings were more frequent in patients taking Rosuvastatin 40 mg, when compared to lower doses of Rosuvastatin or comparator HMG-CoA reductase inhibitors, though it was generally transient and was not associated with worsening renal function. Although the clinical significance of this finding is unknown, a dose reduction should be considered for patients on Rosuvastatin therapy with unexplained persistent proteinuria and/or hematuria during routine urinalysis testing.
Endocrine Effects: Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including Rosuvastatin. Based on clinical trial data with Rosuvastatin, in some instances these increases may exceed the threshold for the diagnosis of diabetes mellitus.
Although clinical studies have shown that Rosuvastatin alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if Rosuvastatin is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.
Lactation: There are no data with respect to excretion in milk in humans. Rosuvastatin is contraindicated in lactation.

FERTILITY, 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 toxicit. 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 DRUG REACTIONS:
The most common side effects of Rosuvastatin are headache, nausea, vomiting, diarrhea and muscle pain. The most serious side effects are liver failure, muscle breakdown (rhabdomyolysis) and kidney failure. Liver failure caused by statins is very rare. More often, statins cause increase in liver tests due to injury to the liver.

DRUG INTERACTIONS:
Rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent.
Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter organic anion-transporting polyprotein 1B1 (OATP1B1) and efflux transporter breast cancer resistance protein (BCRP). Concomitant administration of Rosuvastatin with medications that are inhibitors of these transporter proteins (e.g., cyclosporine, certain HIV protease inhibitors) may result in increased Rosuvastatin plasma concentrations and an increased risk of myopathy.

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. 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.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph. Seek medical attention immediately at the first sign of any adverse drug reaction.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

AVAILABILITY:
Alu/Alu Blister Pack x 7's (Box of 28's and 98's) and Alu/Alu Blister Pack x 10's (Box of 100's)

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