RAPIVAST 5
Rosuvastatin Tablets 5 mg

COMPOSITION:
Each film coated tablet contains:
Rosuvastatin Calcium
Eq. to Rosuvastatin 5 mg
Excipients q. s.
Colour: Ferric Oxide of Red USP & Titanium Dioxide BP

DESCRIPTION:
Rosuvastatin Tablets 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 Tablets is a Orange coloured, round, biconvex film coated tablet plain on both sides.

PHARMACODYNAMIC:
Pharmacotherapeutic group: HMG-CoA reductase inhibitors
ATC code: C10AA07
Mechanism of actions:
Rosuvastatin is a selective, potent 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. Triglycerides (TG) and cholesterol in the liver are incorporated, with apolipoprotein B (ApoB), into very low density lipoprotein (VLDL) and released into the plasma for delivery to peripheral tissues. VLDL particles are TG-rich. Cholesterol-rich low density lipoprotein (LDL) is formed from VLDL and is cleared primarily through the high affinity LDL receptor in the liver.
Rosuvastatin produces its lipid-modifying effects in two ways; it 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.

PHARMACOKINETIC:
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%). In vitro metabolism studies using human hepatocytes indicate that 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.
Excretion:
Approximately 90% of the Rosuvastatin dose is excreted unchanged in the faeces (consisting of absorbed and non-absorbed active substance) 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.

INDICATION:
Rosuvastatin Tablet should be used as an adjunct to diet when the response to diet and exercise is inadequate.
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 Tablet is indicated to:
- Reduce the risk of nonfatal myocardial infarction
- Reduce the risk of nonfatal stroke
- Reduce the risk of coronary artery revascularisation

Hypercholesterolaemia
Rosuvastatin Tablet is indicated to:
- Reduce elevated LDL-C, total cholesterol, triglycerides and to increase HDLcholesterol in patients with primary hypercholesterolaemia (heterozygous familial and non familial) and mixed dyslipidaemia (Fredrickson Types IIa and Iib). Rosuvastatin Tablet also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG, the LDL-C/HDL-C, total C/HDL-C, nonHDL-C/HDL-C, ApoB/ApoA-I ratios and increases ApoA-I in these populations.
- Treat isolated hypertriglyceridaemia (Fredrickson Type IV hyperlipidaemia).
- Reduce total cholesterol and LDL-C in patients with homozygous familial hypercholesterolaemia, as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or alone if such treatments are unavailable. Prior to initiating therapy with rosuvastatin, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.

POSOLOGY AND METHOD OF ADMINISTRATION:
Rosuvastatin Tablet may be given at any time of the day, with or without food.
Before treatment initiation the patient should be placed on a standard cholesterol-lowering diet that should continue during treatment. The dose should be individualised according to the goal of therapy and patient response, using current consensus guidelines.
Treatment of hypercholesterolaemia
The recommended start dose is 5 or 10 mg orally once daily in both statin naïve or 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.
Prevention of cardiovascular events
In the cardiovascular events risk reduction study, the dose used was 20 mg daily.
Paediatric population
Paediatric 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 hypercholesterolaemia 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 paediatric patients, as recommended by the paediatric 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.
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 hypercholesterolaemia. Therefore, Rosuvastatin Tablets 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 use of Rosuvastatin Tablets 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 Tablets is contraindicated in patients with active liver disease
Method of Administration: Oral

SPECIAL WARNING AND PRECAUTION FOR USE:
Liver:
Liver function tests should be performed before initiation of treatment and periodically thereafter. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of rosuvastatin is recommended. As with other HMG-CoA reductase inhibitors, Rosuvastatin Tablet should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease.
Skeletal muscle:
As with other HMG-CoA reductase inhibitors, effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis, have been reported in patients treated with rosuvastatin. As with other HMG-CoA reductase inhibitors, the reported rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose. Patients who develop any signs or symptoms suggestive of myopathy should have their CK levels measured. Rosuvastatin Tablet therapy should be discontinued if CK levels are markedly elevated (>10xULN) or if myopathy is diagnosed or suspected. There have been very rare reports of an immune-mediated necrotizing myopathy clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase during treatment or following discontinuation of statins, including rosuvastatin. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required. Rosuvastatin Tablet was dosed with any concomitant therapy. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other HMGCoA reductase inhibitors together with ciclosporin, fibric acid derivatives, including gemfibrozil, nicotinic acid, azole antifungals and macrolide antibiotics. Rosuvastatin Tablet should be prescribed with caution in patients with pre-disposing factors for myopathy, such as renal impairment, advanced age and hypothyroidism, or situations where an increase in plasma levels may occur. Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Rosuvastatin Tablet should 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, major surgery, trauma, severe, metabolic, endocrine and electrolyte disorders; or uncontrolled seizures).
Diabetes mellitus:
There is sufficient evidence to support an association between statin use and newonset type 2 diabetes mellitus; however the risk appears to be mainly in patients already at increased risk of developing type 2 diabetes. Risk factors for the development of type 2 diabetes include raised fasting blood glucose, history of hypertension, raised triglycerides and raised body mass index. Patients at risk should be monitored both clinically and biochemically according to national guidelines. There is insufficient evidence to confirm or exclude an increased risk for any individual statin or a dose-response relationship and the cardiovascular benefits of statin therapy continue to outweigh the risk of developing type 2 diabetes. As with other HMG-CoA reductase inhibitors, increases in HbA1c and serum glucose levels have been observed in patients treated with Rosuvastatin and in some instances these increases may exceed the threshold for the diagnosis of diabetes mellitus, primarily in patients already at high risk for developing diabetes
Race:
Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians
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 (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.
Children and adolescents 6 to 17 years of age:
The evaluation of linear growth (height), weight, BMI (body mass index) and secondary characteristics of sexual maturation by Tanner staging in paediatric patients taking Rosuvastatin Tablet is limited to a two year period.

CONTRAINDICATION:
Rosuvastatin Tablet is contraindicated in patients with hypersensitivity to any component of this product.
Rosuvastatin Tablet is contraindicated in patients with active liver disease or persistent, unexplained elevations in transaminases.
Rosuvastatin Tablet is contraindicated during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures.

INTERACTION WITH OTHER MEDICINE AND CONCOMITANT USE:
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 Tablets 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 Tablets and Ciclosporin, Rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers. Rosuvastatin Tablet 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 Tablets and some protease inhibitor combinations may be considered after careful consideration of Rosuvastatin Tablets dose adjustments based on the expected increase in Rosuvastatin exposure.
Gemfibrozil and other lipid-lowering products: Concomitant use of Rosuvastatin Tablets and Gemfibrozil resulted in a 2-fold increase in Rosuvastatin Cmax 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. These patients should also start with the 5 mg dose.
Ezetimibe: A pharmacodynamic interaction, in terms of adverse effects, between Rosuvastatin Tablets and ezetimibe cannot be ruled out.
Antacid: The simultaneous dosing of Rosuvastatin Tablets with an antacid suspension containing Aluminium and magnesium hydroxide resulted in a decrease in Rosuvastatinplasma concentration of approximately 50%. This effect was mitigated when the antacid was dosed 2 hours after Rosuvastatin Tablets. The clinical relevance of this interaction has not been studied.
Erythromycin: Concomitant use of Rosuvastatin Tablets 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: 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: When it is necessary to co-administer Rosuvastatin Tablets with other medicinal products known to increase exposure to Rosuvastatin, doses of Rosuvastatin Tablet should be adjusted. Start with a 5 mg once daily dose of Rosuvastatin Tablets, if the expected increase in exposure (AUC) is approximately 2-fold or higher.

PREGNACY AND LACTATION:
Rosuvastatin Tablet 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 foetus, 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 REACTION:
The adverse reactions seen with Rosuvastatin Tablets are generally mild and transient. In controlled clinical trials, less than 4% of Rosuvastatin Tablets-treated patients were withdrawn due to adverse reactions.
Renal effects: Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with Rosuvastatin Tablets. 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. 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.
Haematuria has been observed in patients treated with Rosuvastatin Tablets 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 Tablets-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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
Studies to determine the effect of Rosuvastatin Tablets on the ability to drive and use machines have not been conducted. However, based on its pharmacodynamic properties, Rosuvastatin Tablets is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

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.

INCOMPATIBILITY:
None

SHELF LIFE:
36 Months

PACKAGING:
10 tablets are packed in Alu-Alu Blister in 10 monocarton & 10 such monocartons are packed in outer carton along with pack insert.

STORAGE CONDITION:
Store in a dry place below 30°C.
Keep out of reach of children.

MM Reg. No. : 2411AA5375

MARKETED BY:
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