xxxxxxxx-8883

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

ROSUCOR

(Rosuvastatin Calcium Tablets 10mg and 20mg)

COMPOSITION:
Rosuvastatin Calcium Tablets 10mg:
Each film coated tablet contains:
Rosuvastatin Calcium equivalent to
Rosuvastatin 10mg
Rosuvastatin Calcium Tablets 20mg:
Each film coated tablet contains:
Rosuvastatin Calcium equivalent to
Rosuvastatin 20mg

CLINICAL PHARMACOLOGY:
Pharmacodynamics:
Rosuvastatin is a 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitor indicated for the treatment of hyperlipidemia. Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase. HMG-CoA reductase is a rate-limiting enzyme that converts 3-hyd roxy-3-methylglutary l coenzyme Ato mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering. It differs structurally from other statins, containing a polar methane sulphonamide group which confers relative hydrophilicity. The relative hydrophilicity of rosuvastatin imparts greater selectivity for uptake into hepatic versus non hepatic cells. 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. In preclinical studies, the potency of rosuvastatin has been found to be greater than that of other statins (i.e. atorvastatin, simvastatin, pravastatin, lovastatin, cerivastatin, and fluvastatin). 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. It also lowers the LDL-C/ HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.
Pharmacokinetics:
Absorption: Oral rosuvastatin appears to be well absorbed. Maximum rosuvastatin plasma concentrations are achieved approximately 3-5 hours after oral administration. Peak plasma levels and AUC values are approximately linear over the dose range of 5-80 mg.
Distribution: Rosuvastatin is taken up extensively by hepatic versus non-hepatic tissue attributed to its relative hydrophilicity. The volume of distribution of rosuvastatin is approximately 134 L.
Metabolism: Rosuvastatin undergoes limited metabolism (about 10%), primarily via cytochrome P 450 isoenzymes 2C9 and 2C19; there is essentially no metabolism by cytochrome P 450-3A4, indicating a low propensity for drug interactions compared to other statins. It is mainly metabolized to the N-desmethyl metabolite and the lactone metabolite.
The N-desmethyl metabolite is the active metabolite. Rosuvastatin accounts for greater than 90% of the circulating HMG-CoA reductase inhibitor activity.
Excretion: Approximately 90% of rosuvastatin is excreted as unchanged drug in the faeces and the remaining part is excreted in urine. The plasma elimination half-life is 13-20 hours. The elimination half-life is not dose dependent.
Special populations:
Age and sex: There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin.
Renal insufficiency: The pharmacokinetics is not affected by mild to moderate renal impairment.
Hepatic insufficiency: The pharmacokinetics is not affected by mild to moderate hepatic impairment.

INDICATIONS AND USAGE:
- Primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) as an adjunct to diet when response to diet and exercise is inadequate.
- Mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and exercise is inadequate.
- Homozygous familial hypercholesterolaemia, either alone or as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) when response to diet and exercise is inadequate.

CONTRAINDICATIONS:
- Prior hypersensitivity to Rosuvastatin
- Pregnant and lactating females
- Patients with Acute liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminases elevation exceeding 3 x the upper limit of normal (ULN).
- Patients with severe renal impairment (Renal Clearance < 30ml/min.)
- Patients with myopathy.
- Patients receiving concomitant Cyclosporine.

PRECAUTIONS:
General:
Rosuvastatin should be used with precaution in:
- Patients with history of hypersensitivity to other statins.
- Patients who consume excessive quantities of alcohol, patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3x the upper limit of normal. It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of treatment with rosuvastatin.
- Patients with myopathy. Uncomplicated myalgia and myopathy have been reported in rosuvastatin treated patients. Patients should be asked to report inexplicable muscle pain or weakness immediately, particularly if associated with malaise or fever. Creatininine Kinase (CK) levels should be measured in these patients. Rosuvastatin therapy should be discontinued if CK levels are markedly elevated (>10xULN) or, if on clinical grounds, myopathy is diagnosed or suspected.
- Patients receiving concomitant cyclosporin.
- 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).
- Rosuvastatin is not expected to affect the ability to drive or use machines.

Carcinogenesis, mutagenesis, impairment of fertility:
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity potential. In a rat pre and postnatal study, reproductive toxicity was evident from reduced litter sizes, litter weight and pup survival. These effects were observed at maternally toxic doses at systemic exposures several times above the therapeutic exposure level.
Pregnancy: Teratogenic Effects:
Rosuvastatin should not be used during pregnancy as the safety of rosuvastatin during pregnancy has not been established. Women of childbearing potential should use adequate birth-control measures when rosuvastatin is used. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having sensitivity down to at least 50 mIU/mL for hCG should be obtained prior to rosuvastatin therapy. 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. If a patient becomes pregnant during use of this product, treatment should be discontinued immediately.
Nursing Mothers:
Rosuvastatin should not be used during lactation as the safety of rosuvastatin during lactation has not been established. Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion in milk in humans.
Pediatric Use:
Pediatric experience is limited to a small number of children (aged 8 years or above) with homozygous familial hypercholesterolaemia. Use in children should be supervised by specialists.

DRUG INTERACTIONS:
Rosuvastatin appears to have a low propensity for pharmacokinetic drug interactions. In vitro, metabolism of rosuvastatin was found to be inhibited by sulphaphenazole and to a lesser extent omeprazole, indicating that cytochrome P450 2C9 and 2C19 are the primary metabolic enzymes. In a well designed study in 18 healthy volunteers the co-administration of rosuvastatin with digoxin did not significantly affect the pharmacokinetics of digoxin. Renal clearance of digoxin was 5% higher when co-administered with rosuvastatin.
In volunteers, neither erythromycin nor ketoconazole nor fluconazole have any clinically relevant effect on the pharmacokinetics of a single dose of rosuvastatin 80mg. Furthermore, increases observed in the plasma concentration of rosuvastatin when co-administered with either fenofibrate or itraconazole are unlikely to be of clinical significance.
Vitamin K antagonists (e.g. warfarin or another coumarin anticoagulant) with rosuvastatin may result in an increase in International Normalised Ratio (INR). Discontinuation of treatment may result in a decrease in INR. Concomitant use of Rosuvastatin and Gemfibrozil and other lipid-lowering products resulted in increased exposure.

ADVERSE REACTIONS:
The adverse events seen with rosuvastatin are generally mild and transient. Commonly occurring adverse events are pharyngitis, headache, dizziness, constipation, nausea, abdominal pain, asthenia and myalgia. As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to increase with increasing dose.
Skeletal Muscle Effects: Rare cases of rhabdomyolysis have been reported in subjects receiving rosuvastatin 80 mg in investigational clinical trials which were occasionally associated with impairment of renal function. All cases improved on cessation of therapy.
Laboratory Effects: As with other HMG-CoA reductase inhibitors, a dose-related increase in transaminases and CK has been observed in a small number of patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient. Proteinuria has been observed in patients treated with rosuvastatin.

OVERDOSAGE:
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.

DOSAGE AND ADMINISTRATION:
Adult dose:
The usual start dose is Rosuvastatin 5-10 mg once daily and the majority of patients are controlled at this dose. A dose adjustment to 20 mg can be made after 4 weeks, if necessary. Rosuvastatin 40 mg should only be used in patients with severe hypercholesterolaemia (including those with familial hypercholesterolaemia) who do not achieve their treatment goal on 20 mg. Rosuvastatin may be given at any time of day, with or without food. The patient should be placed on a standard cholesterol-lowering diet that should continue during treatment.
Pediatric Use:
Pediatric experience is limited to a small number of children (aged 8 years or above) with homozygous familial hypercholesterolaemia. Use in children should be supervised by specialists.
Geriatric Use: No dose adjustment required.
Dosage in patients with renal insufficiency:
No dose adjustment is necessary in patients with mild to moderate renal impairment. For patients with severe renal impairment (Cr. Cl. <30 ml/min) the dose of rosuvastatin should not exceed 10 mg once daily.
Dosage in patients with hepatic impairment:
No dose adjustment is necessary in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment the dose of rosuvastatin should not exceed 20 mg once daily.
Dosage in patient with hepatic impairment:
Increase 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 consider. There is no experience in subjects with Child-Pugh scores above 9. ROSUCOR is contraindicated in patients with active liver disease.
Concomitant Therapy:
The effect of ROSUCOR on LDL-C and Total-C may be enhanced when used in combination with Gemfibrozil; the dose of ROSUCOR should be limited to 10mg once daily.

EXPIRY DATE
Do not use later than expiry date.

STORAGE:
Store below 30^{o}C. Protect from moisture and light.

PRESENTATIONS:
ROSUCOR Tablets are available in Alu-Alu blister strip of 10 tablets.

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Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.