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

ROZUCOR ASP
(Rosuvastatin and Aspirin Capsules)

COMPOSITION:

ROZUCOR ASP-5

Each hard gelatin capsule contains:
Rosuvastatin Calcium I.P.
Equivalent to Rosuvastatin 5 mg (as film-coated tablet) Colours: Red Oxide of Iron and Titanium Dioxide I.P. Aspirin I.P. 75 mg (as enteric coated tablet)
Color: Yellow Oxide of Iron
Approved colours used in hard gelatin capsule shell

ROZUCOR ASP-10

Each hard gelatin capsule contains:
Rosuvastatin Calcium I.P.
Equivalent to Rosuvastatin 10 mg (as film-coated tablet) Colors: Red Oxide of Iron and Titanium Dioxide I.P. Aspirin I.P. 75 mg (as enteric coated tablet)
Colour: Yellow Oxide of Iron
Approved colours used in hard gelatin capsule shell

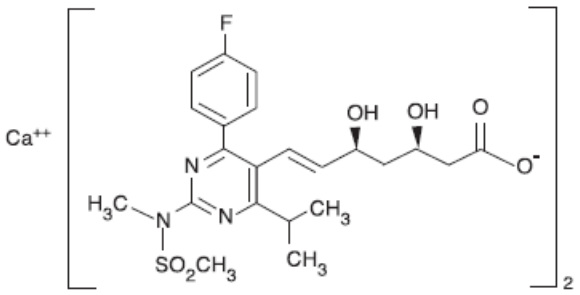
ROZUCOR ASP-10 FORTE

Each hard gelatin capsule contains:
Rosuvastatin Calcium I.P.
Equivalent to Rosuvastatin 10 mg (as film-coated tablet) Colors: Red Oxide of Iron and Titanium Dioxide I.P. Aspirin I.P. 150 mg (as enteric coated tablet)
Colour: Yellow Oxide of Iron
Approved colours used in hard gelatin capsule shell

DESCRIPTION:

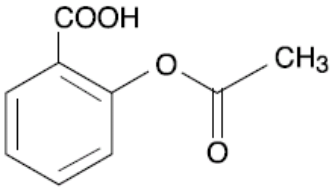
Rosuvastatin

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 for cholesterol. Rosuvastatin Calcium is (*E*)-(3*R*,*5S*)-7-{4-(4-fluorophenyl)-6-isopropyl -2-[methyl(methylsulphonylamino)]pyrimidin-5-yl}-3,5-dihydroxy hepten-6-oic acid calcium. Rosuvastatin Calcium has empirical formula $(C_{22}H_{27}FN_3O_6S)_2.Ca$ calculated on the anhydrous basis. Its molecular weight is 1001.1.



Aspirin

Aspirin is 2-Acetoxy benzoic acid. Its empirical formula is C9H8O4 and Molecular weight is 180.2. Structural Formula:



CLINICAL PHARMACOLOGY:

PHARMACODYNAMICS:

Rosuvastatin

Rosuvastatin is a 3-hydroxy-3-methyl glutaryl coenzyme A (HMGCoA) 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-hydroxy-3-methyl glutaryl coenzyme A to 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 nonhepatic 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. A therapeutic effect is obtained within 1 week following treatment initiation and 90% of maximum response is achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

Aspirin:

Acetylsalicylic acid (ASA) interferes with the production of prostaglandins in various organs and tissues through acetylation of the enzyme cyclooxygenase. The inhibition of platelet aggregation by ASA is due to its abilityto interfering with the production of thromboxane A2 within the

platelet. Thromboxane A2 is, largely, responsible for the aggregating properties of platelets. Platelets play an important role in normal hemostasis and clinical pathologic and experimental evidence indicates that their aggregation mayplay an equally important role in the evolution of a variety of disease statesincluding cerebrovascular disease, ischemic heart disease and myocardialinfarction. Aspirin inhibits platelet aggregation by irreversibly acetylating platelet cyclo-oxygenase, thereby blocking the production of prostaglandin endoperoxides PGG2 and PGH2 which are precursors of the major platelet-aggregating material, thromboxane A2, which is also a powerful vasoconstrictor. However, aspirin does not prevent the adherence of platelets to damaged vessel walls or the release of granule contents from these adherent platelets. As the anuclear platelets are unable to synthesize new enzyme molecules to replace those that have been inactivated, inhibition of platelet aggregation by aspirin thus persists for the life of the platelets.

Besides inhibiting the biosynthesis of thromboxane A2 by platelets, aspirin also interferes with the production of prostacyclin (PGI2) by vascular endothelial cells, the above-mentioned prostaglandin endoperoxides being common precursors of both thromboxane A2 and prostacyclin. This latter compound is one of the most powerfully acting platelet deaggregators and vasodilators and thus it would appear that the interference with the hemostatic processes by aspirin depends on the thromboxane-prostacyclin balance. In fact, it has been suggested that under some conditions, high doses of aspirin may be thrombogenic. However, in contrast to platelets, the vascular endothelial cells are able to regenerate cyclo-oxygenase in a relatively short time and therefore therapeutic doses of aspirin are likely to produce a lesser inhibition of the vascular prostacyclin system than of the platelet thromboxane-forming mechanism.

In fact, there is no clinical evidence to indicate that high doses of aspirin would result in an increased risk of thromboembolism.Absorption of non-ionised aspirin occurs in the stomach and intestine. Some aspirin is hydrolysed to salicylate in the gut wall. After absorption aspirin is rapidly converted to salicylate but during the first 20 minutes following oral administration, aspirin is the predominant form of the drug in the plasma. Aspirin is bound to plasma proteins and is widely distributed. Plasma aspirin concentrations decline rapidly (half life 15-20 minutes) as plasma salicylate concentrations increase. Salicylate is mainly eliminated by hepatic metabolism - the metabolites including salicylic acid, salicyl phenolic glucuronide, salicylic acyl glucuronide, gentisic acid and gentisuric acid.

As a result of zero order kinetics, plasma steady state salicylate concentrations increase disproportionately with dose. Salicylate is also excreted unchanged in the urine to an extent which depends on the dosage and urinary pH. Renal excretion involves glomerular filtration, active renal tubular secretion and passive tubular reabsorption.

PHARMACOKINETICS:

Rosuvastatin

Absorption:

The absolute bioavailability of Rosuvastatin is approximately 20%. Administration of Rosuvastain with food did not affect the AUC of Rosuvastatin. The AUC of Rosuvastain does not differ following evening or morning drug administration. 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 nonhepatic tissue attributed to its relative hydrophilicity. The volume of distribution of rosuvastatin is approximately 134 L. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.

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.

Linearity:
Systemic exposure of rosuvastatin increases in proportion to dose. There are no changes in pharmacokinetic parameters following multiple daily doses.

Race:
Pharmacokinetic studies show an approximate 2-fold elevation in median AUC and Cmax in Asian subjects (Japanese, Chinese, Filipino, Vietnamese and Koreans) compared with Caucasians; Asian-Indians show an approximate 1.3-fold elevation in median AUC and Cmax. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics between Caucasian and Black groups.

Special populations:
Age and sex:
There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin.

Renal Impairment:
The pharmacokinetics is not affected by mild to moderate renal impairment. However, plasma concentrations of rosuvastatin increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment (CLcr less than 30 mL/min/1.73 m^2) not receiving hemodialyis compared with healthy subjects (CLcr greater than 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, C_{max} and AUC were increased by 60% and 5%, respectively, as compared with patients with normal liver function. In patients with Child-Pugh B disease, C_{max} and AUC were increased 100% and 21%, respectively, compared with patients with normal liver function. A therapeutic effect is obtained within 1 week following treatment initiation and 90% of maximum response is achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

Aspirin:
Absorption: Aspirin is well and completely absorbed from the gastrointestinal (GI) tract and is hydrolyzed to salicylic acid with peak plasma levels ofsalicylic acid seen within 1-2 hours of dosing. The rate of absorption isdependent upon the dosage form, the presence or absence of food, gastric pH, and other physiologic factors. The gastric mucosa is permeable to the non-ionized form of acetylsalicylic acid, which passes through the stomach wall by a passive diffusion process. Optimum absorption of salicylate in the human stomach occurs in the pH range of 2.15 to 4.10. Absorption in the small intestine occurs at a significantly faster rate than in the stomach.

Distribution: Salicylic acid is widely distributed to all tissues and fluids in the body including the central nervous system (CNS), breast milk, and fetaltissues, with highest concentrations seen in plasma, liver, renal cortex, heart, and lungs. The protein binding of salicylate is non-linear; at low concentrations (< 100 mcg/mL), approximately 90% is bound to albumin while at higher concentrations (> 400 mcg/mL), only about 75% is bound.

Metabolism: Aspirin is hydrolyzed rapidly by esterases in the gastrointestinal mucosa and the liver to salicylic acid. The half-life of aspirin in the circulation is from 13 to 19 minutes so that the blood level drops quickly after absorption is complete. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number ofminor metabolites (gentisic acid and other hydroxybenzoic acids).

Excretion: Excretion of salicylates occurs principally via the kidney, through a combination of glomerular filtration and tubular excretion. Followingtherapeutic doses, excretion is in the form of free salicylic acid, salicyluricacid, as well as phenolic and acyl glucuronides. Salicylate can be detected in the urine shortly after its ingestion but the full dose requires up to 48 hours for complete elimination. The rate of excretion of free salicylate is extremely variable, reported recovery rates in human urine ranging from 10% to 85%, depending largely on urinary pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from < 5% to > 80%. The half-life of salicylic acid is approximately 6 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form salicyluric acid and phenolic glucuronide. Following toxic doses (10-20 gm), the

plasma half-life may be increased to over 20 hours. The elimination of salicylic acid follows zero order pharmacokinetics.

INDICATIONS AND USAGE:
For the treatment of dyslipidemia associated with artherssclerotic arterial disease with risk of myocardial infarction, stroke or peripheral vascular disease.

DOSAGE AND ADMINISTRATION:
Adults: The advice of a doctor should be sought before commencing therapy for the first time. The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with FDC of Rosuvastatin and aspirin. Route of administration is oral and the capsules must not be chewed or crushed. The dose should be individualised according to the goal of therapy and patient response, using current consensus guidelines. This product is administered once daily dose but the dosage should not be increased than maximum allowed dose for individual agents. The maximum dose rosuvastatin is 40mg once daily and for Aspirin for long term use is 75-150mg daily. In some circumstances a higher dose of Aspirin may be appropriate, especially in the short term, and up to 300 mg a day may be used on the advice of a doctor.

Use in the elderly:
A start dose of 5 mg of rosuvastatin 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 for rosuvastatin is necessary in patients with mild to moderate renal impairment. The recommended start dose is 5 mg rosuvastatin in patients with moderate renal impairment (creatinine clearance of < 60 ml/min). The use of rosuvastatin 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 is contraindicated in patients with active liver disease.

CONTRAINDICATIONS:
- Hypersensitivity to rosuvastatin, aspirin, other salicylates or any other NSAIDs or any of the excipients of this medicinal product.
- A history of, or active peptic ulceration, haemophilia or other clotting disorders, gout, asthma, urticaria, rhinitis or other evidence of hyper sensitivity to aspirin or non steroidal anti-inflammatory drugs.

- In patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 x the upper limit of normal (ULN).
- In patients with severe renal impairment (creatinine clearance < 30 ml/min).
- In patients with myopathy
- In patients receiving concomitant ciclosporin
- During pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.
- In children under 12 years

WARNINGS AND PRECAUTIONS

Rosuvastatin

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, coadministered with colchicine, and caution should be exercised when prescribing Rosuvastatin with colchicines.

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 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.

Aspirin
There is a possible association between aspirin and Reye's syndrome when given to children. Reye's syndrome is a very rare disease, which affects the brain and liver, and can be fatal. For this reason aspirin should not be given to children aged less than 12 years unless specifically indicated (e.g. Kawasaki's disease). Aspirin and other NSAIDs may cause salt and water retention and renal failure especially in patients with pre-existing renal impairment. Caution should be exercised in patients with asthma and other allergic conditions, bleeding tendencies, significant anemia, hypoprothrombinemia, impairmentof hepatic or renal function and dehydration.

USE IN SPECIFIC POPULATIONS
Rosuvastatin
Pregnancy Teratogenic effects: Pregnancy Category X.
Rosuvastatin is contraindicated in women who are or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol products are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hyperlipidemia therapy. There are no adequate and well-controlled studies of Rosuvastatin in pregnant women. There have been rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors. In a review of about 100 prospectively followed pregnancies in women exposed to other HMG-CoA reductase inhibitors, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate expected in the general population. However, this study was only able to exclude a three-to-fourfold increased risk of congenital anomalies over background incidence. In 89% of these cases, drug treatment started before pregnancy and stopped during the first trimester when pregnancy was identified.

Rosuvastatin crosses the placenta in rats and rabbits. In rats, Rosuvastatin was not teratogenic at systemic exposures equivalent to a human therapeutic dose of 40 mg/day. At 10-12 times the human dose of 40 mg/day, there was decreased pup survival, decreased fetal body weight among female pups, and delayed ossification. In rabbits, pup viability decreased and maternal mortality increased at doses equivalent to the human dose of 40 mg/day.

Rosuvastatin may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking Rosuvastatin, the patient should be apprised of the potential risks to the fetus and the lack of known clinical benefit with continued use during pregnancy.

Nursing Mothers
It is not known whether rosuvastatin is excreted in human milk, but a small amount of another drug in this class does pass into breast milk. In rats, breast milk concentrations of rosuvastatin are three times higher than plasma levels; however, animal breast milk drug levels may not accurately reflect human breast milk levels. Because another drug in this class passes into human

milk and because HMG-CoA reductase inhibitors have a potential to cause serious adverse reactions in nursing infants, women who require Rosuvastatin treatment should be advised not to nurse their infants.

Pediatric Use
The safety and effectiveness of Rosuvastatin in patients 10 to 17 years of age with heterozygous familial hypercholesterolemia were evaluated in a controlled clinical trial of 12 weeks duration followed by 40 weeks of open-label exposure. Patients treated with 5 mg, 10 mg, and 20 mg daily Rosuvastatin had an adverse experience profile generally similar to that of patients treated with placebo. Although not all adverse reactions identified in the adult population have been observed in clinical trials of children and adolescent patients, the same warnings and precautions for adults should be considered for children and adolescents. There was no detectable effect of Rosuvastatin on growth, weight, BMI (body mass index), or sexual maturation in pediatric patients (10 to 17 years of age). Adolescent females should be counseled on appropriate contraceptive methods while on Rosuvastatin therapy. Rosuvastatin has not been studied in controlled clinical trials involving prepubertal patients or patients younger than 10 years of age. Doses of Rosuvastatin greater than 20 mg have not been studied in the pediatric population.

In children and adolescents with homozygous familial hypercholesterolemia experience is limited to eight patients (aged 8 years and above).

In a pharmacokinetic study, 18 patients (9 boys and 9 girls) 10 to 17 years of age with heterozygous FH received single and multiple oral doses of Rosuvastatin. Both Cmax and AUC of rosuvastatin were similar to values observed in adult subjects administered the same doses.

Geriatric Use
Of the 10,275 patients in clinical studies with Rosuvastatin, 3159 (31%) were 65 years and older, and 698 (6.8%) were 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.
Elderly patients are at higher risk of myopathy and Rosuvastatin should be prescribed with caution in the elderly.

Renal Impairment
Rosuvastatin exposure is not influenced by mild to moderate renal impairment (CLcr $\geq$ 30 mL/min/1.73 m2); however, exposure to rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment who are not receiving hemodialysis. Rosuvastatin dosing should be adjusted in patients with severe renal impairment (CLcr < 30 mL/min/1.73 m2) not requiring hemodialysis.

Hepatic Impairment
Rosuvastatin is contraindicated in patients with active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels. Chronic alcohol liver disease is known to increase rosuvastatin exposure; Rosuvastatin should be used with caution in these patients.

Asian Patients
Pharmacokinetic studies have demonstrated an approximate 2-fold increase in median exposure to rosuvastatin in Asian subjects when compared with Caucasian controls. Rosuvastatin dosage should be adjusted in Asian patients.

Aspirin
Pregnancy:
Pregnant women should only take aspirin if clearly needed. Because of the known effects of NSAIDs on the fetal cardiovascular system (closure of the ductus arterlosus), use during the third trimester of pregnancy should be avoided. Salicylate products have also been associated with alterations in maternal and neonatal hemostasis mechanisms, decreased birth weight, and with perinatal mortality.

Labor and Delivery:
Aspirin should be avoided 1 week prior to and during labor and delivery because it can result in excessive blood loss at delivery. Prolonged gestation and prolonged labor due to prostaglandin inhibition have been reported.

Nursing Mothers:
Nursing mothers should avoid using aspirin because Salicylate is excreted in breast milk. Use of high doses may lead to rashes, platelet abnormalities, and bleeding in nursing infants.

Paediatric population:
There is a possible association between aspirin and Reye's syndrome when given to children. Reye's syndrome is a very rare disease, which affects the brain and liver and can be fatal. For this reason aspirin should not be given to children under 12 years unless specifically indicated (e.g. Kawasaki's disease).

DRUG INTERACTIONS:
Rosuvastatin
Cyclosporine
Cyclosporine increased rosuvastatin exposure (AUC) 7fold. Therefore, in patients taking cyclosporine, the dose of Rosuvastatin should not exceed 5 mg once daily.

Gemfibrozil
Gemfibrozil significantly increased rosuvastatin exposure. Due to an observed increased risk of myopathy/rhabdomyolysis, combination therapy with Rosuvastatin and gemfibrozil should be avoided. If used together, the dose of Rosuvastatin should not exceed 10 mg once daily.

Protease Inhibitors
Coadministration of rosuvastatin with certain protease inhibitors given in combination with ritonavir has differing effects on rosuvastatin exposure. The protease inhibitor combinations lopinavir/ritonavir and atazanavir/ritonavir increase rosuvastatin exposure (AUC) up to threefold. For these combinations the dose of Rosuvastatin should not exceed 10 mg once daily. The

combinations of tipranavir/ritonavir or fosamprenavir/ritonavir produce little or no change in rosuvastatin exposure. Caution should be exercised when rosuvastatin is coadministered with protease inhibitors given in combination with ritonavir.

Coumarin Anticoagulants
Rosuvastatin significantly increased INR in patients receiving coumarin anticoagulants. Therefore, caution should be exercised when coumarin anticoagulants are given in conjunction with Rosuvastatin. 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.

Niacin
The risk of skeletal muscle effects may be enhanced when Rosuvastatin is used in combination with lipid-modifying doses (≥1 g/day) of niacin; caution should be used when prescribing with Rosuvastatin.

Fenofibrate
When Rosuvastatin was coadministered with fenofibrate, no clinically significant increase in the AUC of rosuvastatin or fenofibrate was observed. Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concomitant use of fenofibrates, caution should be used when prescribing fenofibrates with Rosuvastatin.

Colchicine
Cases of myopathy, including rhabdomyolysis, have been reported with HMG-CoA reductase inhibitors, including rosuvastatin, coadministered with colchicine, and caution should be exercised when prescribing Rosuvastatin with colchicine

Aspirin
Alcohol and corticosteroids may enhance the effects of aspirin on the gastrointestinal tract. Aspirin may enhance the effects of coumarinanticoagulant, oral hypoglycaemics (of the sulphonylurea type), Phenytoin and sodium valproate. Aspirin may increase the risk of bleeding with other antiplatlet drugs such as clopidogrel and ticlopidine. The toxicity of methotrexate may be enhanced by concomitant use of aspirin. Aspirin 75mg may antagonise the diuretic effect of spironolactone and may reduce acetazolamide excretion (risk of toxicity). Aspirin increases plasma concentration of zafirlukast. Metoclopramide and domperidone enhance the effect of aspirin (increased rate of absorption). Avoid concomitant administration with mifepristone (theoretical interaction). Aspirin diminishes the action of uricosurics. Aspirin may reduce the efficacy of antihypertensive drugs. Aspirin is pharmaceutically incompatible with iron salts and alkalis. Avoid concomitant administration of antacids and absorbents (excretion of aspirin is increased in alkaline urine whilst kaolin may reduce absorption). This product should be administered cautiously for such conditions.

ADVERSE REACTIONS:
Rosuvastatin

- Rhabdomyolysis with myoglobinuria and acute renal failure and myopathy (including myositis)
- Liver enzyme abnormalities

In the Rosuvastatin controlled clinical trials database (placebo or active-controlled) of 5394 patients with a mean treatment duration of 15 weeks, 1.4% of patients discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were:

- Myalgia
- Abdominal pain
- Nausea
- Headache
- Myalgia
- Abdominal pain
- Asthenia
- Nausea

The most commonly reported adverse reactions (incidence ≥ 2%) in the Rosuvastatin controlled clinical trial database of 5394 patients were:

Clinical Studies Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

Adverse reactions reported in ≥ 2% of patients in placebo-controlled clinical studies and at a rate greater than placebo are shown in Table 1. These studies had treatment duration of up to 12 weeks.

Adverse Reactions* Reported in ≥ 2% of Patients Treated with Rosuvastatin and > Placebo in Placebo-Controlled Trials (% of Patients)

Adverse Reactions	Rosuvastatin 5 mg N=291	Rosuvastatin 10 mg N=283	Rosuvastatin 20 mg N=64	Rosuvastatin 40 mg N=106	Total Rosuvastatin 5 mg – 40mg N=744	Placebo N=382
Headache	5.5	4.9	3.1	8.5	5.5	5.0
Nausea	3.8	3.5	6.3	0	3.4	3.1
Myalgia	3.1	2.1	6.3	1.9	2.8	1.3
Asthenia	2.4	3.2	4.7	0.9	2.7	2.6
Constipation	2.1	2.1	4.7	2.8	2.4	2.4

* Adverse reactions by COSTART preferred term.

Other adverse reactions reported in clinical studies were abdominal pain, dizziness, hypersensitivity (including rash, pruritus, urticaria, and angioedema) and pancreatitis. The following laboratory abnormalities have also been reported: dipstick-positive proteinuria and microscopic hematuria; elevated creatine phosphokinase, transaminases, glucose, glutamyl transpeptidase, alkaline phosphatase, and bilirubin; and thyroid function abnormalities.

In the METEOR study, involving 981 participants treated with rosuvastatin 40 mg (n=700) or placebo (n=281) with a mean treatment duration of 1.7 years, 5.6% of subjects treated with Rosuvastatin versus 2.8% of placebo--treated subjects discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were: myalgia, hepatic enzyme increased, headache, and nausea.

Adverse reactions reported in ≥ 2% of patients and at a rate greater than placebo are shown in Table.

Adverse Reactions* Reported in ≥ 2% of Patients Treated with Rosuvastatin and > Placebo in the METEOR Trial (% of Patients)

Adverse Reactions	**Rosuvastatin 40 mg N=700**	**Placebo N=281**
Myalgia	12.7	12.1
Arthralgia	10.1	7.1
Headache	6.4	5.3
Dizziness	4.0	2.8
Increased CPK	2.6	0.7
Abdominal pain	2.4	1.8
†ALT >3x ULN	2.2	0.7

* Adverse reactions by MedDRA preferred term.
† Frequency recorded as abnormal laboratory value.

In the JUPITER study, 17,802 participants were treated with rosuvastatin 20 mg (n=8901) or placebo (n=8901) for a mean duration of 2 years. A higher percentage of rosuvastatin-treated patients versus placebo-treated patients, 6.6% and 6.2%, respectively, discontinued study medication due to an adverse event, irrespective of treatment causality. Myalgia was the most common adverse reaction that led to treatment discontinuation.

In JUPITER, there was a significantly higher frequency of diabetes mellitus reported in patients taking rosuvastatin (2.8%) versus patients taking placebo (2.3%). Mean HbA1c was significantly increased by 0.1% in rosuvastatin-treated patients compared to placebo-treated patients. The number of patients with a HbA1c > 6.5% at the end of the trial was significantly higher in rosuvastatin-treated versus placebo-treated patients.

Adverse reactions reported in ≥ 2% of patients and at a rate greater than placebo are shown in Table

Adverse Reactions* Reported in ≥ 2% of Patients Treated with Rosuvastatin and > Placebo in the JUPITER Trial (% of Patients)

Adverse Reactions	Rosuvastatin 20 mg N=8901	Placebo N=8901
Myalgia	7.6	6.6
Arthralgia	3.8	3.2
Constipation	3.3	3.0
Diabetes mellitus	2.8	2.3
Nausea	2.4	2.3

* Treatment-emergent adverse reactions by MedDRA preferred term

Pediatric patients 10 to 17 years of age

In a 12-week controlled study in boys and postmenarchal girls, the safety and tolerability profile of Rosuvastatin 5 to 20 mg daily was generally similar to that of placebo.

However, elevations in serum creatine phosphokinase (CK) > 10 x ULN were observed more frequently in rosuvastatin compared with placebo-treated children. Four of 130 (3%) children treated with rosuvastatin (2 treated with 10 mg and 2 treated with 20 mg) had increased CK > 10 x ULN, compared to 0 of 46 children on placebo.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Rosuvastatin: arthralgia, fatal and non-fatal hepatic failure, hepatitis, jaundice, thrombocytopenia, depression, sleep disorders (including insomnia and nightmares), peripheral neuropathy and gynecomastia. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

There have been rare reports of immune-mediated necrotizing myopathy associated with statin use.

There has been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Aspirin

Many adverse reactions due to aspirin ingestion are dose-related. The following is a list of adverse reactions that have been reported in the literature

Body as a whole: Fever, hypothermia, thirst.

Cardiovascular: Dysrhythmias, hypotension, tachycardia.

Central nervous system: Agitation, Cerebral edema, coma, confusion, dizziness, headache, subdural or intracranial hemorrhage, lethargy, seizures. Fluid and Electrolyte: Dehydration, hyperkalemia, membolic acidosis, respiratory alkalosis.

Gastrointestinal: Dyspepsia, GI bleeding, ulceration and perforation, nausea, vomiting, heartburn, transient elevations of hepatic enzymes, hepatitis, Reye's syndrome, pancreatitis.

Hematologic: Prolongation of the prothrombin time, disseminated intravascular coagulation, coagulopathy, thrombocytopenia, anaemia, purpura, leucopenia

Dermatologic and hypersensitivity: Acute anaphylaxis, angioedema, asthma,bronchospasm, laryngeal edema, , pruritus, skin eruptions, urticaria.

Musculoskeletal: Rhabdomyolysis.

Metabolism: Hypoglycemia (in children), hyperglycemia.

Reroductive: Prolonged pregnancy and labor, stillbirths, lower birth weight infants, antepartum and postpartum bleeding.

Respiratory: Hyperpnea, pulmonary edema, tachypnea.

Special Senses: Hearing loss, vertigo, tinnitus. Patients with higher frequency hearing loss may have difficulty perceiving tinnitus. In these patients, tinnitus cannot be used as a clinical indicator of salicylism.

Urogenital: Interstitial nephritis, papillary necrosis, proteinuria, renal insufficiency and failure.

OVERDOSAGE:

Rosuvastatin

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.

Aspirin

Common features of overdose include dizziness, tinnitus, deafness, vasodilation and sweating, nausea and vomiting, headache and mental confusion. If more severe, hyperventilation, fever, restlessness, ketosis, respiratory alkalosis and metabolic acidosis. Coma, if severe, with cardiovascular collapse and respiratory failure. Hypoglycaemia may be severe in children. Overdosage should be treated initially by aspiration and lavage and a saline purgative such as sodium sulphate, 30g in 250ml ofwater should be given to promote peristalsis. Otherwise treat as for aspirinpoisoning and observe for at least 72 hours to allow for possible delayed reaction from gastro-resistant system. Restoration of acid-base balance may be necessary.

STORAGE:

Store at a temperature not exceeding 25^{o}C, protected from light and moisture. Keep out of reach of children.

Expiry Date:

Do not use later than the date of expiry.

PRESENTATIONS:
Rozucor ASP-5, Rozucor ASP-10 and Rozucor ASP-10 Forte are available in strip pack of 10 capsules.

WARNING:
Not to be used in children below 12 years of age except under medical advice.

Do not take this product during the last three months of pregnancy unless directed by a doctor. Aspirin taken near the time of delivery may cause bleeding problems to both mother and child.

MARKETED BY

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