ROZTOR- A Capsules

(Rosuvastatin calcium + Aspirin)

Prescribing Information

Composition

ROZTOR- A75

Each hard gelatin capsule contains:
Composition:
Rosuvastatin Calcium...IP (As granules)
equivalent to Rosuvastatin.....10 mg

Aspirin IP .....75 mg
(As enteric coated granules)

Dosage Form

Capsule

Description

ROZTOR- A Capsules are a fixed-dose combination of rosuvastatin and aspirin.

Pharmacology

Pharmacodynamics

Rosuvastatin

Rosuvastatin is a selective and competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme that converts HMG-CoA 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 low-density lipoprotein (LDL) receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, rosuvastatin inhibits hepatic synthesis of very-low-density lipoprotein (VLDL), which reduces the total number of VLDL and LDL particles.

Rosuvastatin reduces elevated LDL-cholesterol (LDL-C), total cholesterol (total C) and triglycerides (TG) and increases high density lipoprotein cholesterol (HDL-C). It also lowers apolipoprotein (Apo) B, non-HDL-C, VLDL-cholesterol, VLDL-TG and increases ApoA-1. Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and non-HDL-C/HDL-C and the ApoB/ApoA-1 ratios.

Aspirin

Aspirin is a more potent inhibitor of both prostaglandin synthesis and platelet aggregation than other salicylic acid derivatives. The differences in activity between aspirin and salicylic acid are thought to be due to the acetyl group on the aspirin molecule. This acetyl group is responsible for the inactivation of cyclo-oxygenase via acetylation.

Aspirin affects platelet aggregation by irreversibly inhibiting prostaglandin cyclo-oxygenase. This effect lasts for the life of the platelet and prevents the formation of the platelet-aggregating factor thromboxane A_2. Non-acetylated salicylates do not inhibit this enzyme and have no effect on platelet aggregation. At somewhat higher doses, aspirin reversibly inhibits the formation of prostaglandin I_2 (prostacyclin), which is an arterial vasodilator and inhibits platelet aggregation.

At higher doses, aspirin is an effective anti-inflammatory agent, partially due to inhibition of inflammatory mediators via cyclo-oxygenase inhibition in peripheral tissues. *In vitro* studies suggest that other mediators of inflammation may also be suppressed by aspirin administration, although the precise mechanism of action has not been elucidated. It is this non-specific suppression of cyclo-oxygenase activity in peripheral tissues following large doses that leads to its primary side effect of gastric irritation.

Pharmacokinetics

Absorption

In clinical pharmacology studies in man, peak plasma concentrations of rosuvastatin were reached 3 to 5 hours following oral dosing. Both peak concentration (C_{max}) and area under the plasma concentration-time curve (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.

Enteric-coated aspirin products are erratically absorbed from the GI tract. Hydrolysis to salicylic acid occurs in the intestine and in the circulation. The rate of absorption from the GI tract is dependent upon the dosage form, the presence or absence of food, gastric pH (the presence or absence of GI antacids or buffering agents) and other physiologic factors.

Distribution

Rosuvastatin is taken up extensively by the liver, which is the primary site of cholesterol synthesis and LDL-C clearance. 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.

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

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 (CYP450) 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.

Aspirin is rapidly hydrolyzed in the plasma to salicylic acid such that plasma levels of aspirin are essentially undetectable 1 to 2 hours after dosing. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylic acid has a plasma half-life of approximately 6 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (10 to 20 g), the plasma half-life may be increased to over 20 hours.

Excretion

Following oral administration, approximately 90% of rosuvastatin and its metabolites are primarily excreted in the feces (consisting of absorbed and non-absorbed active substance) while the rest is excreted in the urine. Approximately 5% is excreted unchanged in urine. The elimination half-life ($t_{1/2}$) of rosuvastatin is approximately 19 hours. The elimination half-life does not increase at higher doses. After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route.

The elimination of salicylic acid follows zero-order pharmacokinetics (i.e. the rate of drug elimination is constant in relation to plasma concentration). Renal excretion of unchanged drug depends upon urine pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from <5% to >80%. Alkalization of the urine is a key concept in the management of salicylate overdose. Following therapeutic doses, approximately 10% is found excreted in the urine as salicylic acid, 75% as salicyluric acids, and 10% and 5% as the phenolic and acyl glucuronides, respectively.

Special Populations

Geriatric: There were no differences in plasma concentrations of rosuvastatin between the non-elderly and elderly populations (age ≥65 years).

Gender: There were no differences in plasma concentrations of rosuvastatin between men and women.

Renal Impairment: Mild to moderate renal impairment 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 (CL_{cr} <30 mL/min/1.73 m^2) not receiving hemodialysis compared with healthy subjects (CL_{cr} >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.

Race: A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups, However, pharmacokinetic studies have demonstrated an approximate 2-fold elevation in median exposure (AUC and C_{max}) in Asian subjects when compared with a Caucasian control group. Asian-Indians show an approximate 1.3-fold elevation in median AUC and C_{max}.

Pharmacogenomics

Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, involves organic anion-transporting polypeptide (OATP) 1B1 and other transporter proteins. Higher plasma concentrations of rosuvastatin have been reported in very small groups of patients (n=3 to 5) who have reduced function alleles of the gene that encodes OATP1B1 (*SLCO1B1* 521T>C). The frequency of this genotype (i.e. *SLCO1B1* 521 C/C) is generally lower than 5% in most racial/ethnic groups. The impact of this polymorphism on efficacy and/or safety of rosuvastatin has not been clearly established. Doses should be titrated according to patient response and tolerability.

Indications

ROZTOR- A (rosuvastatin and aspirin) is indicated for the treatment of dyslipidemia associated with artherosclerotic arterial disease with risk of myocardial infarction, stroke or peripheral vascular disease.

Rosuvastatin

Hyperlipidemia and Mixed Dyslipidemia

Rosuvastatin is indicated as adjunctive therapy to diet to reduce elevated total cholesterol (total-C), LDL cholesterol (LDL-C), apoprotein B (ApoB), non-high-density lipoprotein cholesterol (nonHDL-C), and triglycerides (TG) and to increase high-density lipoprotein cholesterol (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 non-pharmacological interventions alone has been inadequate.

Pediatric Patients 10 to 17 Years of Age with Heterozygous Familial Hypercholesterolemia (HeFH)

Adjunct to diet to reduce total-C, LDL-C and ApoB levels in adolescent boys and girls, who are at least one year post-menarche, 10-17 years of age with HeFH, if after an adequate trial of diet therapy the following findings are present: LDL-C >190 mg/dL or >160 mg/dL and there is a positive family history of premature cardiovascular disease (CVD) or two or more other CVD risk factors.

Hypertriglyceridemia

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

Primary Dysbetalipoproteinemia (Type III Hyperlipoproteinemia)

Rosuvastatin is indicated as adjunctive therapy to diet for the treatment of patients with primary dysbetalipoproteinemia (Type III hyperlipoproteinemia).

Homozygous Familial Hypercholesterolemia

Rosuvastatin 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

Rosuvastatin 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 CVD

In individuals without clinically evident coronary heart disease but with an increased risk of CVD based on age $\geq$50 years old in men and $\geq$60 years old in women, hsCRP $\geq$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, rosuvastatin is indicated to:

- reduce the risk of stroke;
- reduce the risk of myocardial infarction; and,
- reduce the risk of arterial revascularization procedures.

Aspirin

Vascular Indications
Aspirin is indicated to

- Reduce the combined risk of death and non-fatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli.
- Reduce the risk of vascular mortality in patients with a suspected acute MI.
- Reduce the combined risk of death and non-fatal MI in patients with a previous MI or unstable angina pectoris.
- Reduce the combined risk of MI and sudden death in patients with chronic stable angina pectoris.

Revascularization Procedures

Aspirin is indicated in patients who have undergone revascularization procedures (i.e. CABG, PTCA or carotid endarterectomy) when there is a pre-existing condition for which aspirin is already indicated.

Dosage and Administration

Patients should be placed on an appropriate lipid-lowering diet before receiving ROZTOR- A, and should continue this diet during treatment. The recommended dosage is one or two capsules once daily.

The dose of rosuvastatin can be individualized according to baseline LDL-C levels, the goal of therapy and patient response. After initiation or upon titration of rosuvastatin, lipid levels should be analyzed within 2 to 4 weeks and the dosage adjusted accordingly. The maximum dose is 40 mg once daily.

The maximum dose of aspirin in patients with unstable angina pectoris, chronic stable angina pectoris and for prevention of recurrent acute myocardial infarction, ischemic stroke and TIA, coronary artery bypass graft, percutaneous transluminal coronary angioplasty is 325 mg once a day.

Contraindications

- Hypersensitivity to rosuvastatin, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), salicylic acid compounds, prostaglandin synthetase inhibitors or to any of the excipients
- Patients with the syndrome of asthma with rhinitis and/or nasal polyps as aspirin may cause severe urticaria, angioedema or bronchospasm (asthma)
- Active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels
- Active, or history of recurrent peptic ulcer and/or gastric/intestinal hemorrhage or other kinds of bleeding such as cerebrovascular hemorrhages
- Hemorrhagic diathesis, coagulation disorders such as hemophilia and thrombocytopenia
- In children or teenagers for viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses.
- In patients with myopathy
- In patients receiving concomitant cyclosporine
- Methotrexate used at doses >15 mg/week
- Severe renal impairment
- Women who are pregnant or may become pregnant
- Lactation

Warnings and Precautions

Drug Interactions

Transporter Protein Inhibitors : Rosuvastatin is a substrate for certain transporter proteins including hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of ROZTOR- A with medicinal products that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy.

***Gemfibrozi l*:** Gemfibrozil significantly increased rosuvastatin exposure. Due to an observed increased risk of myopathy/rhabdomyolysis, combination therapy with ROZTOR- A and gemfibrozil should be avoided. If used together, the dose of rosuvastatin in ROZTOR- A should not exceed 10 mg once daily.

Cyclosporine : Concomitant administration of NSAIDs and cyclosporine may increase the nephrotoxic effect of cyclosporine. During concomitant administration of rosuvastatin and cyclosporine, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers. Therefore, in patients taking cyclosporine, the dose of rosuvastatin should not exceed 5 mg once daily. Hence ROZTOR- A is contraindicated in patients receiving concomitant cyclosporine.

Protease Inhibitors : Co-administration 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. In patients taking these combinations, the dose of ROZTOR- A 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 ROZTOR- A is co-administered with protease inhibitors given in combination with ritonavir.

Anticoagulant Therapy : Rosuvastatin significantly increased International Normalized Ratio (INR) in patients receiving coumarin anticoagulants. Patients on anticoagulation therapy are at increased risk for bleeding because of drug–drug interactions and the effect on platelets. Aspirin can displace warfarin from protein binding sites, leading to prolongation of both the prothrombin time and the bleeding time. Aspirin can increase the anticoagulant activity of heparin, increasing bleeding risk. Concomitant therapy of ROZTOR- A and anticoagulants is not recommended, unless strictly indicated as it may increase the risk of hemorrhage. If the combination cannot be avoided, INR should be determined before starting ROZTOR- A and frequently enough during early therapy to ensure that no significant alteration of INR occurs. Also close observation for signs of bleeding is recommended.

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; thus caution should be exercised when prescribing with ROZTOR- A.

Fenofibrate: When rosuvastatin was co-administered 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 fenofibrate, caution should be exercised when prescribing fenofibrate with ROZTOR- A.

Ezetimibe: Concomitant use of rosuvastatin (10 mg) and ezetimibe (10 mg) resulted in a 1.2-fold increase in AUC and a 30% decrease in C_{max} of rosuvastatin in hypercholesterolemic subjects. A pharmacodynamic interaction, in terms of adverse effects, between rosuvastatin and ezetimibe cannot be ruled out.

Antacids: The simultaneous dosing of rosuvastatin with an antacid suspension containing aluminum 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. The clinical relevance of this interaction has not been studied. The excretion of aspirin may be increased by alkaline urine, which can occur with some antacids.

Erythromycin: Concomitant use of rosuvastatin and erythromycin resulted in a 20% decrease in AUC and a 30% decrease in C_{max} of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.
CYP450 enzymes: Results from *in vitro* and *in vivo* studies show that rosuvastatin is neither an inhibitor nor an inducer of CYP450 isoenzymes. In addition, rosuvastatin is a poor substrate for these isoenzymes. Therefore, drug interactions resulting from CYP450-mediated metabolism are not expected. No clinically relevant interaction have been observed between rosuvastatin and either fluconazole (an inhibitor of CYP2C9 and CYP3A4) or ketoconazole (an inhibitor of CYP2A6 and CYP3A4).

Oral Contraceptives/Hormone Replacement Therapy (HRT): 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. There are no pharmacokinetic data available in subjects taking concomitant rosuvastatin and HRT and therefore a similar effect cannot be excluded. However, the combination has been extensively used in women in clinical trials and was well tolerated.

Fusidic Acid: Interaction studies with rosuvastatin and fusidic acid have not been conducted. As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with rosuvastatin and fusidic acid given concurrently. Therefore, the combination of ROZTOR- A and fusidic acid is not recommended. If possible, temporary suspension of ROZTOR- A treatment is recommended. If unavoidable, patients should be closely monitored.

Digoxin: Based on data from specific interaction studies, no clinically relevant interaction of rosuvastatin with digoxin is expected. However, aspirin impairs the renal excretion of digoxin, resulting in increased plasma concentrations. Monitoring of plasma concentrations of digoxin is recommended when initiating and terminating treatment with ROZTOR- A. Dose adjustment may be necessary.

Colchicine: 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 ROZTOR-A with colchicine.

Clopidogrel: Concomitant administration of rosuvastatin with clopidogrel has shown to increase the AUC of rosuvastatin by 2-fold.

Eltrombopag: Concomitant administration of rosuvastatin with this drug has shown to increase the AUC of rosuvastatin by 1.6-fold.

Dronedarone: Co-administration of rosuvastatin with dronedarone has shown to increase the AUC of rosuvastatin by 1.4-fold.

Itraconazole: Concomitant administration of rosuvastatin with itraconazole has shown to increase the AUC of rosuvastatin by 1.4-fold.

Baicalin: Administration of rosuvastatin along with baicalin has shown to decrease the AUC of rosuvastatin by 47%.
Lithium: Aspirin impairs the renal excretion of lithium, resulting in increased plasma concentrations. Monitoring of plasma concentrations of lithium is recommended when initiating and terminating treatment with ROZTOR- A. Dose adjustment may be necessary.

Tacrolimus: Concomitant administration of NSAIDs and tacrolimus may increase the nephrotoxic effect of tacrolimus. The renal function should be monitored in case of concomitant use of tacrolimus and ROZTOR- A.
Angiotensin-converting Enzyme (ACE) Inhibitors: The hyponatremic and hypotensive effects of ACE inhibitors may be diminished by the concomitant administration of aspirin due to its indirect effect on the renin-angiotensin conversion pathway.

Carbonic Anhydrase Inhibitors (Acetazolamide): Concurrent use of aspirin and acetazolamide can lead to high serum concentrations of acetazolamide (and toxicity) due to competition at the renal tubule for secretion. It may result in severe acidosis and increased central nervous system toxicity.

Anticonvulsants: Salicylate can displace protein-bound phenytoin and valproic acid, leading to decrease in the total concentration of phenytoin and an increase in serum valproic acid levels.

Beta-blockers: The hypotensive effects of beta-blockers may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt and fluid retention.
Diuretics: There is risk of acute renal failure due to decreased glomerular filtration via decreased renal prostaglandin synthesis. Hydrating the patient and monitoring renal function at the start of the treatment is recommended. The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow, and salt and fluid retention.

Methotrexate: Salicylate can inhibit renal clearance of methotrexate, leading to bone marrow toxicity especially in the elderly or renally impaired.

NSAIDs: Concomitant therapy of ROZTOR- A with other NSAIDs is not recommended, unless strictly indicated as it may increase the risk of hemorrhage. If the combination cannot be avoided, close observation for signs of bleeding is recommended.

Oral Hypoglycemics/Insulin: Moderate dose of aspirin may increase the effectiveness of oral hypoglycemic drugs and insulin, leading to hypoglycemia.

Systemic Corticosteroids: Use ROZTOR- A with caution in patients on oral corticosteroids as it could increase the risk of gastrointestinal (GI) ulceration and bleeding.

Anti-platelet Agents: Concurrent administration of aspirin with drugs such as clopidogrel or dipyridamole is associated with an increased risk of GI bleeding. Concomitant therapy of ROZTOR- A and anti-platelet agents is not recommended, unless strictly indicated as it may increase the risk of hemorrhage. If the combination cannot be avoided, close observation for signs of bleeding is recommended.

Thrombolytic Agents: Concomitant therapy of ROZTOR- A and thrombolytic agents is not recommended, unless strictly indicated as it may increase the risk of hemorrhage. If the combination cannot be avoided, close observation for signs of bleeding is recommended.

Selective Serotonin-Re-uptake Inhibitors (SSRIs): Concomitant therapy of ROZTOR- A and SSRIs is not recommended, unless strictly indicated as it may increase the risk of hemorrhage. If the combination cannot be avoided, close observation for signs of bleeding is recommended. Concomitant use of ROZTOR- A and SSRIs could also increase the risk of ulceration.

Deferasirox: Use ROZTOR- A with caution in patients on deferasirox as concomitant use could increase the risk of ulceration.

Uricosuric Agents (Probenecid and Sulfinpyrazone): Salicylates antagonize the uricosuric action of uricosuric agents.

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).

ROZTOR- A 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 ROZTOR- A 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 ROZTOR- A with colchicine.

ROZTOR- A therapy should be discontinued if markedly elevated creatine kinase (CK) levels occur or myopathy is diagnosed or suspected. ROZTOR- A 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 CK, 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 physicians unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing ROZTOR- A.

Liver Enzyme Abnormalities

It is recommended that liver enzyme tests be performed before the initiation of ROZTOR- A therapy, and if signs or symptoms of liver injury occur.

Increases in serum transaminases 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 (ULN) 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 ROZTOR- A, promptly interrupt therapy. If an alternate etiology is not found, do not restart ROZTOR-A.

Active liver disease, which may include unexplained persistent transaminase elevations, is a contraindication to the use of ROZTOR- A.

Concomitant Coumarin Anticoagulants

Concomitant therapy of ROZTOR- A and anti-coagulants is not recommended, unless strictly indicated as it may increase the risk of hemorrhage. If the combination cannot be avoided, INR should be determined before

starting ROZTOR- A and frequently enough during early therapy to ensure that no significant alteration of INR occurs. Also close observation for signs of bleeding is recommended.

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 ROZTOR- A therapy with unexplained persistent proteinuria and/or hematuria during routine urinalysis testing.

Endocrine Effects/Diabetes Mellitus

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. Patients at risk (fasting glucose 5.6 to 6.9 mmol/l, body mass index (BMI) >30 kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines. In the JUPITER study, the reported overall frequency of diabetes mellitus was 2.8% in rosuvastatin and 2.3% in placebo, mostly in patients with fasting glucose 5.6 to 6.9 mmol/l. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping ROZTOR-A treatment.

Although clinical studies have shown that rosuvastatin alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if ROZTOR- A is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

Asian Patients

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

Alcohol

Patients who consume three or more alcoholic drinks every day should be counselled about the bleeding risks involved with chronic, heavy alcohol use while taking ROZTOR- A. ROZTOR- A should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of chronic liver disease.

Protease Inhibitors

Increased systemic exposure to rosuvastatin has been observed in subjects receiving rosuvastatin concomitantly with various protease inhibitors in combination with ritonavir. Consideration should be given both to the benefit of ROZTOR- A in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up-titrating ROZTOR- A doses in patients treated with protease inhibitors. The concomitant use with certain protease inhibitors is not recommended unless the dose of rosuvastatin in ROZTOR-A is adjusted.

Lactose Intolerance

ROZTOR- A should be avoided in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Interstitial Lung Disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. Presenting features can include dyspnea, non-productive cough and deterioration in general health (fatigue, weight

loss and fever). If it is suspected a patient has developed interstitial lung disease, ROZTOR- A therapy should be discontinued.

Coagulation Abnormalities

Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. This can adversely affect patients with inherited (hemophilia) or acquired (liver disease or vitamin K deficiency) bleeding disorders.

GI Side Effects

GI side effects include stomach pain, heartburn, nausea, vomiting and gross GI bleeding. Although minor upper GI symptoms, such as dyspepsia are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Physicians should inform patients about the signs and symptoms of GI side effects and what steps to take if they occur.

History of Peptic Ulcer Disease/Hemorrhagic Episodes

Patients with a history of active peptic ulcer disease or hemorrhagic episodes should avoid using ROZTOR- A, since aspirin can cause gastric mucosal irritation and bleeding.

Sodium-retaining Disease States

Patients with sodium-retaining states, such as congestive heart failure or renal failure, should avoid sodium-containing buffered aspirin preparations because of their high sodium content.

Surgery/Minor Procedures

Aspirin is associated with an increased risk of hemorrhage particularly during or after operative procedures (even in cases of minor procedures, e.g., tooth extraction). Use ROZTOR- A with caution before surgery, including tooth extraction. Temporary discontinuation of treatment may be necessary.

Menorrhagia

ROZTOR- A is not recommended during menorrhagia where it may increase menstrual bleeding.

Hypersensitivity

Aspirin may promote bronchospasm and asthma attacks or other hypersensitivity reactions. Risk factors are existing asthma, hay fever, nasal polyps or chronic respiratory diseases. The same applies for patients who also show allergic reaction to other substances (e.g., with skin reactions, itching or urticaria).

Serious skin reactions, including Steven-Johnsons syndrome, have rarely been reported in association with the use of aspirin. ROZTOR- A should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Gout

Aspirin especially in low doses may reduce uric acid excretion. Due to this fact, patients who tend to have reduced uric acid excretion may experience gout attacks. Hence, use ROZTOR- A with caution in these patients.

Glucose 6-phosphate Dehydrogenase Deficiency

High doses of aspirin may precipitate acute hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Hence, use ROZTOR- A with caution in these patients.

Renal Impairment

Rosuvastatin exposure is not influenced by mild- to moderate renal impairment ($CL_{cr} \geq 30$ mL/min/1.73 m^2); however, exposure to rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment who are not receiving hemodialysis. Aspirin needs to be avoided in patients with severe renal failure (glomerular filtration rate <10 mL/min). Hence, ROZTOR- A should be used with caution in patients with moderately impaired renal function while it should be avoided in those with severe renal failure.

Hepatic Impairment

Aspirin should be avoided in patients with severe hepatic insufficiency. Liver function tests should be performed regularly in patients presenting slight or moderate hepatic insufficiency. Rosuvastatin is contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels. Thus, ROZTOR- A is contraindicated in patients with active liver disease, including unexplained persistent elevations in hepatic transaminase levels.

Pregnancy

Pregnancy Category X

Rosuvastatin is contraindicated in women who are or may become pregnant. Rosuvastatin may cause fetal harm when administered to a pregnant woman. It is recommended that pregnant women should take aspirin only if clearly needed. Aspirin has the ability to alter platelet function and, therefore, there may be a risk of hemorrhage in infants whose mothers have consumed aspirin during pregnancy. The onset of labor may be delayed and the duration increased, with an increase in maternal blood loss. High doses of aspirin may result in closure of fetal arteriosus in utero and possibly persistent pulmonary hypertension in the new born. Kenicterus may be a consequence of jaundice in neonates.

ROZTOR- A should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking ROZTOR-A, it should be discontinued immediately and the patient should be apprised of the potential risks to the fetus.

Lactation

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. Salicylate is excreted in breast milk. Use of salicylates at high doses may lead to rashes, platelet abnormalities and bleeding in nursing infants. Nursing mothers should avoid using ROZTOR- A. Women who require ROZTOR- A 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 HeFH 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, or sexual maturation in pediatric patients (10 to 17 years of age). Rosuvastatin has not been studied in controlled clinical trials involving pre-pubertal 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).

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

Aspirin is not recommended for use in adolescents/children aged under 16 years unless the expected benefits outweigh the risks. It may be a contributory factor in the causation of Reye's syndrome in some children. ROZTOR- A should be avoided in children below 16 years unless expected benefits outweigh the risks.

Geriatric Use

Of the 10,275 patients in clinical studies with rosuvastatin, 3,159 (31%) were ≥65 years, and 698 (6.8%) were ≥75 years. 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 particularly susceptible to the adverse effects of NSAIDs (including aspirin), especially GI bleeding and perforation, which may be fatal.

Elderly patients are at higher risk of myopathy and GI bleeding and, hence, ROZTOR- A should be prescribed with caution in the elderly.

Undesirable Effects

Rosuvastatin

The following serious adverse reactions are discussed in greater detail in other sections:

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

In the rosuvastatin controlled clinical trials database (placebo or active-controlled) of 5,394 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

The most commonly reported adverse reactions (incidence ≥2%) in the rosuvastatin controlled clinical trial database of 5,394 patients were:

- Headache
- Myalgia
- Abdominal pain
- Asthenia
- Nausea

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.

Table 1: Adverse reactions* reported by >2% of patients treated with rosuvastatin and greater than 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 - 40 mg 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 (Coding Symbols for a Thesaurus of Adverse Reaction Terms) 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 kinase (CK), 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 2.

Table 2: Adverse reactions* reported by >2% of patients treated with rosuvastatin and greater than 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 CK	2.6	0.7
Abdominal pain	2.4	1.8

Adverse Reactions	Rosuvastatin 40 mg N=700	Placebo N=281
ǂAlanine transaminase (ALT) >3x ULN	2.2	0.7

* Adverse reactions by MedDRA (Medical Dictionary for regulatory Affairs) preferred term.
ǂFrequency recorded as abnormal laboratory value.

In the JUPITER study, 17,802 participants were treated with rosuvastatin 20 mg (n=8,901) or placebo (n=8,901) 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 3.
Table 3: Adverse reactions* reported by >2% of patients treated with rosuvastatin and greater than placebo in the JUPITER trial (% of Patients)

Adverse Reactions	Rosuvastatin 20 mg N=8,901	Placebo N=8,901
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 post-menarchal girls, the safety and tolerability profile of rosuvastatin 5 to 20 mg daily was generally similar to that of placebo.

However, elevations in serum CK >10 × 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 × ULN, compared to 0 of 46 children on placebo.

Postmarketing Experience
The following adverse reactions have been identified during post-approval 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 have 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 non-serious 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 are 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, metabolic acidosis, respiratory alkalosis

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

Hematologic: increased bleeding tendencies, prolongation of prothrombin time, disseminated intravascular coagulation, coagulopathy, thrombocytopenia, granulocytosis, aplastic anemia

Hypersensitivity: acute anaphylaxis including shock, angioedema, allergic edema, asthma, bronchospasm, laryngeal edema, urticaria

Metabolism: hypoglycemia (in children), hyperglycemia

Musculoskeletal: rhabdomyolysis

Reproductive: menorrhagia, prolonged pregnancy and labor, stillbirths, low birth weight infants, antepartum and postpartum bleeding

Respiratory: rhinitis, dyspnea, hyperpena, pulmonary edema, tachypnea

Skin: Steven-Johnsons syndrome, Lyells syndrome, purpura, erythema nodosum, erythema multiforme
Special Senses: hearing loss, 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
Vascular: hemorrhagic vasculitis

If you experience any side-effects, talk to your doctor.

Over dosage

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. Hemodialysis does not significantly enhance clearance of rosuvastatin.

Aspirin

Salicylate toxicity may result from acute ingestion (overdose) or chronic intoxication. The early signs of salicylic overdose (salicylism), including tinnitus, occur at plasma concentrations approaching 200 mcg/mL. Plasma concentrations of aspirin above 300 mcg/mL are clearly toxic. Severe toxic effects are associated with levels above 400 mcg/mL. A single lethal dose of aspirin in adults is not known with certainty but death may be expected at 30 g.

Symptoms and Signs

In acute overdose, severe acid-base and electrolyte disturbances may occur and are complicated by hyperthermia and dehydration. Respiratory alkalosis occurs early while hyperventilation is present, but is quickly followed by metabolic acidosis.

Treatment

Treatment consists primarily of supporting vital functions, increasing salicylates elimination, and correcting the acid-base disturbance. Gastric emptying and/or lavage is recommended as soon as possible after ingestion, even if the patient has vomited spontaneously. After lavage and/or emesis, administration of activated charcoal, as slurry, is beneficial, if less than 3 hours have passed since ingestion. Charcoal adsorption should not be employed prior to emesis and lavage.

Severity of aspirin intoxication is determined by measuring the blood salicylates level. Acid-base status should be closely followed with serial blood gas and serum pH measurements. Fluid and electrolyte balance should also be maintained. In severe cases, hyperthermia and hypovolemia are major immediate threats to life. Children should be sponged with tepid water. Replacement fluid should be administered intravenously and augmented with correction of acidosis. Plasma electrolytes and pH should be monitored to promote alkaline diuresis of salicylates if renal function is normal. Infusion of glucose may be required to control hypoglycemia.

Hemodialysis and peritoneal dialysis can be performed to reduce the body drug content. In patients with renal impairment or in cases of life-threatening intoxication, dialysis is usually required. Exchange transfusion may be indicated in infants and young children

Incompatibility

None

Shelf-Life

2 years

Storage and Handling Instructions

Store in a cool, dry and dark place.

Packaging Information

ROZTOR- A75: Strip pack of 10 capsules