R5A / R10A CAPSULES

Rosuvastatin + Enteric coated Aspirin

COMPOSITION

R5A

Each capsule contains:	
Rosuvastatin	5 mg
Enteric coated Aspirin	75 mg

R10A

Each capsule contains:	
Rosuvastatin	10 mg
Enteric coated Aspirin	75 mg

DESCRIPTION

R5A and R10A contains Rosuvastatin and Aspirin based on the latest guidelines by **American Heart Association, Nov 2013** and **American Diabetes Association, Jan 2014 ,** in the Primary prevention of Coronary Artery Diseases in Diabetes and Secondary prevention of Coronary Artery Diseases in Diabetes respectively.

PHARMACOLOGY

Pharmacodynamics:

Rosuvastatin: Rosuvastatin is an inhibitor of HMG-CoA reductase, an enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. Rosuvastatin reduces cholesterol by increasing the number of low-density lipoprotein (LDL) receptors on the cell-surface to enhance uptake and catabolism of LDL. It also inhibits hepatic synthesis of hepatic very-low-density lipoprotein (VLDL), which reduces the total number of VLDL and LDL particles. The treatment reduces triglycerides (TG) and produces increases in high-density lipoprotein cholesterol (HDL-C.)

Aspirin: Adhering and aggregating platelets secrete TXA-2, which leads to further platelet recruitment and activation. TXA-2 is a product of arachidonic acid metabolism and is formed within the activated platelet. TXA-2 formation is catalysed by the enzyme cyclo-oxygenase (COX)-1. Aspirin inactivates COX-1, thereby almost completely abolishing in vitro platelet TXA-2 formation, resulting in reduced platelet function.

Pharmacokinetics:

Absorption:

Rosuvastatin: The absolute bioavailability of Rosuvastatin is approximately 20%.The AUC of Rosuvastatin does not differ following evening or morning drug administration.

Aspirin: Aspirin is rapidly absorbed after oral administration, with some hydrolysis to salicylate before absorption. Absorption is delayed by the presence of food and is impaired in patients suffering migraine attacks. Absorption is more rapid in patients with achlorhydria and also following administration of polysorbates and antacids.

Blood concentration-

Peak plasma concentrations of approximately 45mcg/ml are attained 1 to 2 hours after an oral dose of 640mg, but stabilise at approximately 270mcg/ml after oral doses of 3g daily. After an oral dose of about 2g, peak plasma concentrations of approximately 15mcg/ml of Aspirin are attained in about one hour and peak plasma concentrations of approximately 130mcg/ml of salicylate are attained in 2 to 4 hours.

Half-life: Plasma / Aspirin Approximately 17 minutes

Distribution:

Rosuvastatin: 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 concentration.

Aspirin: Aspirin is found in the saliva, milk, plasma and synovial fluid at concentrations less than blood and crosses the placenta. Salicylate - extensive protein binding. Aspirin - protein binding to a small extent.

Metabolism:

Rosuvastatin: Rosuvastatin is not extensively metabolized; approximately 10% of a radiolabeled dose is recovered as metabolite. The major metabolite is N-desmethyl Rosuvastatin, which is formed principally by cytochrome P450 2C9, and in vitro studies have demonstrated that N-desmethyl Rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of the parent compound. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by the parent compound[1]

Aspirin: In the blood, rapid hydrolysis to salicylic acid; glucuronic acid/glycine conjugation to form glucuronides and salicyluronic acid; oxidation of a small proportion.

Excretion:

Rosuvastatin: Following oral administration, Rosuvastatin and its metabolites are primarily excreted in the feces (90%). The elimination half-life ($t_{1/2}$) of Rosuvastatin is approximately 19 hours. After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route.

Aspirin: Excreted in the urine mainly as salicyluronic acid. Salicylate reabsorbed by renal tubules in acid urine, and alkaline diuresis will increase the rate of excretion; 85% of dose excreted as free salicylate.

INDICATIONS

R5A is indicated for primary prevention of myocardial infarction, stroke, and arterial revascularization procedures in patients **without** clinically evident coronary heart disease but with an increased risk of cardiovascular disease (CVD) based on age (men ≥50 and women ≥60), with the presence of at least one additional CVD risk factor, such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease.

R10A is indicated for secondary prevention of myocardial infarction, stroke, and arterial revascularization procedures in patients **with** coronary heart disease but with an increased risk of cardiovascular disease (CVD) based on age (men ≥50 and women ≥60), with the presence of at least one additional CVD risk factor, such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease.

DOSAGE AND ADMINISTRATION

R5A / **R10A** should be administered once daily after food any time of the day.

CONTRAINDICATIONS

Rosuvastatin: Rosuvastatin is contraindicated in:

- Patients with hypersensitivity to Rosuvastatin or to any of the excipients.
- 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).
- Patients with severe renal impairment (creatinine clearance < 30 ml/min).
- Patients with myopathy.
- Patients receiving concomitant ciclosporin.
- During pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.

Aspirin: Aspirin is contraindicated in:

- Children under 16 years unless specifically indicated (e.g. for Kawasaki's disease).

- Active peptic ulceration or a history of peptic ulceration.
- Haemophilia, other coagulopathies or concurrent anticoagulant therapy.
- Hypersensitivity to Aspirin, any other NSAIDs, or any of the excipients.
- Gout.

WARNING AND PRECAUTIONS

Renal Effects: Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of Rosuvastatin, in particular 40 mg, where it was transient or intermittent in most cases.

Skeletal Muscle Effects: Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in Rosuvastatin and in particular with doses > 20 mg.

Rosuvastatin should not be used in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders; or uncontrolled seizures).

Liver Effects: As with other HMG-CoA reductase inhibitors, Rosuvastatin should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease. Caution should be exercised in patients with asthma, allergic disease, impairment of hepatic or renal function (avoid if severe) and dehydration.

Race: Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians. Use 5 mg/day starting dose in people of Asian ancestry, who may build up higher drug levels and be at higher risk of myopathy.

Protease inhibitors: Increased systemic exposure to Rosuvastatin has been observed in subjects receiving Rosuvastatin concomitantly with various protease inhibitors in combination with ritonavir.

Lactose intolerance: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take **R5A / R10A**.

Interstitial lung disease: Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued. Do not take Aspirin in stomach ulcer.

Diabetes Mellitus: Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk

with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/l, BMI >30 kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines. Aspirin may interfere with insulin and glucagon in diabetes.

Haemolytic anaemia: Caution should be used in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency as haemolytic anaemia may develop. Aspirin prolongs bleeding time, mainly by inhibiting platelet aggregation and therefore it should be discontinued several days before scheduled surgical procedures.

Pregnancy:

Rosuvastatin: Since cholesterol and other products of cholesterol biosynthesis are essential for the development of the foetus, the potential risk from inhibition of HMG-CoA reductase outweighs the advantage of treatment during pregnancy. If a patient becomes pregnant during use of this product, treatment should be discontinued immediately.

Aspirin: There is clinical and epidemiological evidence of the safety of Aspirin in human pregnancy. Aspirin may prolong gestation, delay the onset of or prolong labour and contribute to maternal and neonatal bleeding and is best avoided at term and during breast feeding - possible risk of Reye's Syndrome. Maternal use of Aspirin prior to birth may increase the risk of intracranial haemorrhage in premature or low birth weight infants. The use of Aspirin during pregnancy may cause premature closure of the foetal ductus arteriosus and pulmonary hypertension.

Lactation:

Rosuvastatin: Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion in milk in humans.

Aspirin: Low quantities of salicylates and of their metabolites are excreted into the breast milk. Since adverse effects for the infant have not been reported up to now, short-term use of the recommended dose does not require suspending breastfeeding. In cases of long-term use and/or administration of higher doses, breastfeeding should be discontinued.

Pediatric use:

Rosuvastatin: The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in paediatric patients 10 to 17 years of age taking Rosuvastatin is limited to a one-year period. The clinical trial experience in children and adolescent patients is limited and the long-term effects of Rosuvastatin (>1 year) on puberty are unknown.

Aspirin: Recommended for use in adults and adolescents from 16 years of age. This medicinal product is not recommended for use in adolescents/children under 16 years unless the expected benefits outweigh the risks. Acetylsalicylic acid may be a contributory factor in the causation of Reye's syndrome in some children.

ADVERSE EFFECTS

Side effects are generally mild and infrequent.

Myopathy: In trial using lower doses of Rosuvastatin (5-10mg daily), no cases of myopathy were observed. The Food and Drug Agency (FDA) in the United States has issued a warning regarding Rosuvastatin advising physicians to start doses as low as possible and that maintenance doses of drug should be based on individual cholesterol goals. Other signs and symptoms include muscle pain and weakness, malaise, fever, dark urine, nausea, or vomiting.

Liver toxicity: Another trial using lower doses of Rosuvastatin (5-10mg) recorded that 0.8% of patients studied had ALT levels at three times the upper limit of normal. No cases of liver failure or irreversible liver disease have thus far been reported in clinical trial.

Pharyngitis: Pharyngitis has been reported as occurring in approximately 9% of patients taking Rosuvastatin. It is not clear why this occurs with Rosuvastatin doses. However, other gastrointestinal reactions have been reported – diarrhoea, constipation, stomach upset and nausea which occur in approximately 3% of patients studied.

Other adverse effects reported with Rosuvastatin include headache (5.5%), urinary tract infections (2.3%), rhinitis (2.2%) and sinusitis (2%)

Blood disorders: Aspirin increases bleeding time, decreases platelet adhesiveness and, in large doses, may cause hypoprothrombinaemia. It may also cause other blood disorders including thrombocytopenia.

Haemolytic anaemia can occur in patients with glucose 6-phosphate dehydrogenase deficiency (G6PD).

Immune System: Aspirin may precipitate bronchospasm, and induce asthma attacks, rhinitis, angioedema, or other hypersensitivity reactions in susceptible individuals.

Gastro-intestinal: There is a relatively high incidence of gastro-intestinal irritation with a slight asymptomatic blood loss. Aspirin may induce gastro-intestinal haemorrhage which may occasionally be major.

Skin: Skin reactions may occur in susceptible patients.

DRUG INTERACTION

Rosuvastatin

Cytochrome P450: Rosuvastatin clearance is not dependent on metabolism by CYP 3A4 to a clinically significant extent, thus Rosuvastatin is unlikely to have blood levels increased by drugs which inhibit CYP 3A4 enzyme system.

Cyclosporine: Coadministration of cyclosporine can elevate Rosuvastatin blood levels 11 times that when Rosuvastatin is administered alone. This combination can lead to the possibility of rhabdomyolysis with such high levels of Rosuvastatin.

Gemfibrozil: Coadministration of gemfibrozil can elevate Rosuvastatin blood levels 2 times that when Rosuvastatin is administered alone.

Antacid: Coadministration of cyclosporine with antacids can reduce Rosuvastatin blood levels by 50 per cent. However, when the antacid was administered 2 hours after the Rosuvastatin dose, there were no clinically significant changes in blood levels.

Oral contraceptives: Coadministration of oral contraceptives can elevate ethinyloestradiol levels by 26% and norgestrel levels by 34%, increasing the possibility of adverse effects of these hormones.

Aspirin:

Methotrexate (used at doses >15 mg/week): The combined drugs, methotrexate and acetylsalicylic acid, enhance haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by acetylsalicylic acid.

Uricosuric agents, e.g. probenecid: Salicylates reverse the effect of probenecid. The combination should be avoided.

Anticoagulants e.g. coumarin, heparin, warfarin and phenindione: Increased risk of bleeding due to inhibited thrombocyte function, injury of the duodenal mucosa and displacement of oral anticoagulants from their plasma protein binding sites. The bleeding time should be monitored.

Anti-platelet agents (e.g clopidogrel and dipyridamole) and selective serotonin re-uptake inhibitors (SSRIs; such as sertraline or paroxetine): Increased risk of gastrointestinal bleeding.

Antidiabetics, e.g. sulphonylureas: Salicylics may increase the hypoglycaemic effect of sulphonylureas.

Digoxin and lithium: Acetylsalicylic acid impairs the renal excretion of digoxin and lithium, resulting in increased plasma concentrations. Monitoring of plasma concentrations of digoxin and lithium is recommended when initiating and terminating treatment with acetylsalicylic acid. Dose adjustment may be necessary

Diuretics and antihypertensives: NSAIDs may decrease the antihypertensive effects of diuretics and other antihypertensive agents. As for other NSAIDs concomitant administration with ACE-inhibitors increases the risk of acute renal insufficiency.

Diuretics: Risk of acute renal failure due to the decreased glomerular filtration via decreased renal prostaglandin synthesis. Hydrating the patient and monitoring renal function at the start of the treatment is recommended.

Carbonic anhydrase inhibitors (acetazolamide): May result in severe acidosis and increased central nervous system toxicity

Systemic corticosteroids: The risk of gastrointestinal ulceration and bleeding may be increased when acetylsalicylic acid and corticosteroids are co-administered (see section 4.4).

Other NSAIDs: Increased risk of ulcerations and gastrointestinal bleeding due to synergistic effects.

Ibuprofen: Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly.

Ciclosporin, tacrolimus: Concomitant use of NSAIDs and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin and tacrolimus. The renal function should be monitored in case of concomitant use of these agents and acetylsalicylic acid.

Valproate: Acetylsalicylic acid has been reported to decrease the binding of valproate to serum albumin, thereby increasing its free plasma concentrations at steady state.

Phenytoin (an antiepileptic): Salicylate diminishes the binding of phenytoin to plasma albumin. This may lead to decreased total phenytoin levels in plasma, but increased free phenytoin fraction. The unbound concentration, and thereby the therapeutic effect, does not appear to be significantly altered.

Alcohol: Concomitant administration of alcohol and acetylsalicylic acid increases the risk of gastrointestinal bleeding. Antacids will reduce the effect of Aspirin. Principle incompatibilities are iron salts, carbonates and alkali hydroxides.

OVERDOSE

Rosuvastatin:

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:

Salicylate poisoning is usually associated with plasma concentrations >350mg/L (2.5mmol/L) Most adult deaths occur in patients whose concentrations exceed 700mg/L (5.1mmol/L). Single doses less than 100mg/kg are unlikely to cause serious poisoning.

PRESENTATION

R5A is available in a strip of 10 capsules.

R10A is available in a strip of 10 capsules.

STORAGE

Store in a cool and dry place.