02-09-0390

AURORA

(Rosuvastatin Tablets U.S.P.)

Product Specifications: U.S.P.
Aurora 5 mg Tablets
Each film coated tablet contains: Rosuvastatin calcium U.S.P. eq. to Rosuvastatin ..... 5 mg
Aurora 10 mg Tablets
Each film coated tablet contains: Rosuvastatin calcium U.S.P. eq. to Rosuvastatin ..... 10 mg
Aurora 20 mg Tablets
Each film coated tablet contains: Rosuvastatin calcium U.S.P. eq. to Rosuvastatin ..... 20 mg
Product contains Lactose

DRUG DESCRIPTION:
Rosuvastatin is a synthetic lipid-lowering agent and HMG-CoA Reductase Inhibitor. The chemical name for rosuvastatin calcium is bis[(E)-7-[4-(4-fluorophenyl)-6-isapropyl-2 [methyl (methylsulfonyl) amino] pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt. The empirical formula for rosuvastatin calcium is $(CR_{22}RHR_{27}RFNR_3ROR_6RS)$ R_2RCa and the molecular weight is 1001.14. Rosuvastatin calcium is a white amorphous powder that is sparingly soluble in water and methanol, and slightly soluble in ethanol. Rosuvastatin calcium is a hydrophilic compound with a partition coefficient (octanol/water) of 0.13 at pH of 7.0. (C22H27FN3O6S)2Ca

CLINICAL PHARMACOLOGY
Pharmacotherapeutic group:
Antilipemic Agent, HMG-CoA Reductase Inhibitor
ATC Code: C10AA07
Mechanism of action:
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. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering. Rosuvastatin increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.
Pharmacokinetics:
Absorption:
Peak plasma concentrations of rosuvastatin were reached 3-5 hrs following oral dosing.
Bioavailability:
The absolute bioavailability of rosuvastatin is 20%.
Distribution: The Vd is approximately 134 L
Protein binding: 90%
Metabolism: Hepatic (10%), via CYP2C9 (1 active metabolite identified: N-desmethyl rosuvastatin, one-sixth to one-half the HMG-CoA reductase activity of the parent compound)
Elimination half-life: The elimination half-life (t1/2) is approximately 19 hours.
Excretion: Following oral administration, rosuvastatin and its metabolites are primarily excreted in the feces (90%).
INDICATIONS AND DOSAGE
Indications:
Hyperlipidemia and Mixed Dyslipidemia: AURORA is indicated as adjunctive therapy to diet to reduce elevated Total-C, LDL-C, ApoB, nonHDLC, and triglycerides and to increase 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 nonpharmacological interventions alone has been inadequate.
Pediatric Patients with Familial Hypercholesterolemia
AURORA is indicated as an adjunct to diet to reduce

- Total-C, LDL-C and ApoB levels in children and adolescents 8 to 17 years of age with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy, the following findings are present: LDL-C > 190 mg/dL, or > 160 mg/dL along with a positive family history of premature cardiovascular disease (CVD) or two or more other CVD risk factors.
- Reduce LDL-C, Total-C, nonHDL-C and ApoB in children and adolescents 7 to 17 years of age with homozygous familial hypercholesterolemia, either alone or with other lipid-lowering treatments (e.g., LDL apheresis).

Hypertriglyceridemia: AURORA is indicated as adjunctive therapy to diet for the treatment of adult patients with hypertriglyceridemia.
Primary Dysbetalipoproteinemia (Type III Hyperlipoproteinemia)
AURORA is indicated as an adjunct to diet for the treatment of patients with primary dysbetalipoproteinemia (Type III Hyperlipoproteinemia).
Homozygous Familial Hypercholesterolemia: Rosuvastatin calcium tablets are 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:
Aurora 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 LDLC to target levels.
Primary Prevention of Cardiovascular Disease:
In individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease based on age ≥ 50 years old in men and ≥ 60 years old in women, hsCRP ≥ 2 mg/L, and the presence of at least one additional cardiovascular disease risk factor such as hypertension, low HDLC, smoking, or a family history of premature coronary heart disease, Aurora is indicated to:

- reduce the risk of stroke
- reduce the risk of myocardial infarction
- reduce the risk of arterial revascularization procedures

Limitations of use:
Rosuvastatin calcium tablets have not been studied in Fredrickson Type I and V dyslipidemias.
DOSAGE AND ADMINISTRATION
The dose range for AURORA is 5 mg to 40 mg orally once daily. The usual starting dose is 10 mg to 20 mg. It can be administered as a single dose at any time of day, with or without food. The tablet should be swallowed whole. When initiating rosuvastatin calcium or switching from another HMG-CoA reductase inhibitor therapy, the appropriate starting dose should first be utilized, and only then titrated according to the patient's response and individualized goal of therapy. After initiation or upon titration of rosuvastatin, lipid levels should be analyzed within 2 to 4 weeks and the dosage adjusted accordingly. The 40 mg dose of rosuvastatin calcium tablets should be used only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose.
Homozygous Familial Hypercholesterolemia:
The recommended starting dose of rosuvastatin calcium tablets is 20 mg once daily. Response to therapy should be estimated from preapheresis LDL-C levels.
Prevention of Cardiovascular events:
In the cardiovascular events risk reduction study, the dose used was 20 mg daily.
Primary prevention:
LDL-C ≥ 190 mg/dL: High-intensity therapy: 20 to 40 mg once daily
Type 1 or 2 diabetes and age 40 to 75 years: Moderate-intensity therapy: 5 to 10 mg once daily
Type 1 or 2 diabetes, age 40 to 75 years, and an estimated 10-year ASCVD risk ≥ 7.5%: High intensity therapy: 20 to 40 mg once daily.
Age 40 to 75 years and an estimated 10-year ASCVD risk ≥ 7.5%: Moderate- to high-intensity therapy: 5 to 40 mg once daily.
Secondary prevention:
Patient has clinical ASCVD (e.g., coronary heart disease, stroke/TIA, or peripheral arterial disease presumed to be of atherosclerotic origin) or is post-CABG and
Age ≤ 75 years: High-intensity therapy: 20 to 40 mg once daily
Age > 75 years or not a candidate for high-intensity therapy: Moderate-intensity therapy: 5 to 10 mg once daily.
Pediatric Dosing: Children and adolescents 8 to 17 years of age (Tanner Stage <II-V)
Heterozygous familial hypercholesterolaemia: The usual start dose is 5 mg daily.

- In children 8 to 9 years of age, the usual dose range is 5-10 mg orally once daily. Safety and efficacy of doses greater than 10 mg have not been studied in this population.
- In children 10 to 17 years of age, the usual dose range is 5-20 mg orally once daily. Safety and efficacy of doses greater than 20 mg have not been studied in this population.

Homozygous familial hypercholesterolaemia: In children 7 to 17 years of age, the recommended maximum dose is 20 mg once daily. A starting dose of 5 to 10 mg once daily depending on age, weight and prior statin use is advised. Titration to the maximum dose of 20 mg once daily should be conducted.
Children and adolescents should be placed on standard cholesterol-lowering diet before rosuvastatin treatment initiation; this diet should be continued during rosuvastatin treatment. There is limited experience with doses other than 20 mg in this population. The 40 mg tablet is not suitable for use in pediatric patients.
Dosing in Asian Patients: In Asian patients, consider initiation of rosuvastatin calcium tablets therapy with 5 mg once daily due to increased rosuvastatin plasma concentrations. The increased systemic exposure should be taken into consideration when treating Asian patients not adequately controlled at doses up to 20 mg/day.
Concomitant Lipid-lowering Therapy:
The effect of AURORA on LDL-C and Total-C may be enhanced when used in combination with a bile acid binding resin. Avoid concomitant use of AURORA with gemfibrozil. If concomitant use cannot be avoided, initiate AURORA at 5 mg once daily. The dose of AURORA should not exceed 10 mg once daily. The dose of AURORA should not exceed 5 mg once daily in patients taking cyclosporine and darolutamide. Concomitant use of AURORA and regorafenib, the dose of AURORA should not exceed 10 mg once daily.
Special Population:
Renal Impairment:
CrCl ≥ 30 mL/minute/1.73m^2: No dosage adjustment necessary.
CrCl < 30 mL/minute/1.73m^2: Initial: 5 mg once daily (maximum: 10 mg/day).
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.
Geriatric Use: The overall frequency of adverse events is similar in patients above and below 65 years of age. The efficacy of rosuvastatin in the geriatric population (>65 years of age) is comparable to the efficacy observed in the non-elderly. A start dose of 5 mg is recommended in patients > 70 years. No other dose adjustment is necessary. Elderly patients are at higher risk of myopathy so it should be prescribed with caution in the elderly.
Children younger than 6 years:
The safety and efficacy of use in children younger than 6 years has not been studied. Therefore, rosuvastatin tablets is not recommended for use in children younger than 6 years.
Pregnancy: Category X. Rosuvastatin is contraindicated in women who are or may become pregnant. The ADA Diabetes guidelines recommends avoiding use of HMG-CoA reductase inhibitors in sexually active women of childbearing age who are not using reliable contraception. If treatment of dyslipidemias is needed in pregnant women or in women of reproductive age, other agents are preferred. It should be given to women of childbearing potential only when conception is highly unlikely and patients have been informed of potential hazards.
Nursing Mothers: Rosuvastatin is excreted in breast milk (limited data). Due to the potential for serious adverse reactions in a nursing infant, use while breastfeeding is contraindicated.
Severe muscle symptoms or fatigue: Promptly discontinue use; evaluate CPK, creatinine, and urinalysis for myoglobinuria.
Mild to moderate muscle symptoms: Discontinue use until symptoms can be evaluated; evaluate patient for conditions that may increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases). Upon resolution, resume the original or lower dose of rosuvastatin. If muscle symptoms recur, discontinue rosuvastatin use. After muscle symptom resolution, may then use a low dose of a different statin; gradually increase if tolerated.
Over dosage: 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.

CONTRAINDICATIONS

Rosuvastatin calcium tablets are contraindicated in the following conditions:

- Patients with a known hypersensitivity to any component of this product. hypersensitivity reactions including rash, pruritus, urticaria, and angioedema have been reported with rosuvastatin calcium tablets.
- Patients with active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels.
- Women who are pregnant or may become pregnant.
- Nursing mothers

ADVERSE REACTIONS

>10%

Neuromuscular & skeletal: Myalgia (2% to 13%)

1% to 10%

Central nervous system: Headache (6% to 9%), dizziness (4%)
Endocrine & metabolic: Diabetes mellitus (new onset: 3%)
Gastrointestinal: Nausea (4% to 6%), constipation (3% to 5%)
Genitourinary: Cystitis
Hepatic: Increased serum ALT (2%; >3 times ULN)
Neuromuscular & skeletal: Arthralgia (4% to 10%), increased creatine phosphokinase (3%; >10 x ULN: Children 3%), weakness (5%)

<1%, post marketing, and/or case reports: Abnormal thyroid function test, cognitive dysfunction (reversible; includes amnesia, confusion, memory impairment), depression, elevated glycosylated hemoglobin (HbA), gynecomastia, hematuria (microscopic), hepatic failure, hepatitis, hypersensitivity reaction (including angioedema, pruritus, skin rash, urticaria), immune-mediated necrotizing myopathy, increased gammaglutamyl transferase, increased serum alkaline phosphatase, increased serum bilirubin, increased serum glucose, increased serum transaminases. Interstitial pulmonary disease. Jaundice, myoglobinuria, myopathy, myositis, pancreatitis, peripheral neuropathy, proteinuria (dose related), renal failure, rhabdomyolysis, sleep disorder (including insomnia and nightmares), thrombocytopenia.

WARNINGS AND PRECAUTIONS

Concerns related to adverse effects:

Diabetes mellitus:

Small increases in HbA (mean: ~0.1%) and fasting blood glucose have been reported with rosuvastatin; however, the benefits of statin therapy far outweigh the risk of dysglycemia.

Hematuria/proteinuria: Hematuria (microscopic) and proteinuria have been observed; more commonly reported in adults receiving rosuvastatin 40 mg daily. Typically, transient, and not associated with a decrease in renal function. Consider dosage reduction if unexplained hematuria and proteinuria persists.

Hepatotoxicity: Post marketing reports of fatal and nonfatal hepatic failure are rare. If serious hepatotoxicity with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment, interrupt therapy. If an alternate etiology is not identified, do not restart rosuvastatin. Liver enzyme tests should be obtained at baseline and as clinically indicated; routine periodic monitoring of liver enzymes is not necessary.

Hypersensitivity: Hypersensitivity reactions, including rash, pruritus, urticaria, and angioedema, have been reported.

Immune-mediated necrotizing myopathy (IMNM): IMNM, an autoimmune-mediated myopathy, has been reported (rarely) with HMG-CoA reductase inhibitor therapy. IMNM presents as proximal muscle weakness with elevated CPK levels, which persists despite discontinuation of HMG-CoA reductase inhibitor therapy; additionally, muscle biopsy may show necrotizing myopathy with limited inflammation. Immunosuppressive therapy (e.g., corticosteroids, azathioprine) may be useful for treatment.

Myopathy/rhabdomyolysis: Patients receiving HMG-CoA reductase inhibitors have developed rhabdomyolysis with acute renal failure and/or myopathy; patients should be monitored closely. This risk is dose-related and is increased with concurrent use of other lipid-lowering medications (fibric add derivatives or niacin doses ≥1 g/day), other interacting drugs, other drugs associated with myopathy (e.g., colchicine), age >65 years, female gender, uncontrolled hypothyroidism, and renal dysfunction. Use caution in patients with renal impairment, inadequately treated hypothyroidism, and those taking other drugs associated with myopathy (e.g., colchicine); these patients are predisposed to myopathy. Patients should be instructed to report unexplained muscle pain, tenderness, weakness, or dark urine.

Disease related concerns:

Hepatic impairment and/or ethanol use:

Use with caution in patients who consume large amounts of ethanol or have a history of liver disease. Use is contraindicated with active liver disease or unexplained transaminase elevations.

Renal Impairment: Dosage adjustment required in patients with a CrCl <30 mL/minute/1.73 m and not receiving hemodialysis.

Special populations:

Asian Population: Increased risk of rosuvastatin-associated myopathy in certain subgroups; dosage adjustment should be considered for patients of Asian descent.

Elderly: Use with caution in patients with advanced age; these patients are more predisposed to myopathy.

Surgical patients: It should be temporary discontinue for elective major surgery, acute medical or surgical conditions, or in any patient experiencing an acute or serious condition predisposing to renal failure (e.g., sepsis, hypotension, trauma, uncontrolled seizures). HMG-CoA reductase inhibitors should be continued in the perioperative period for non-cardiac and cardiac surgery. Perioperative discontinuation of statin therapy is associated with an increased risk of cardiac morbidity and mortality.

Other warnings/precautions:

Appropriate use: Secondary causes of hyperlipidemia should be ruled out prior to therapy. Rosuvastatin has not been studied when the primary lipid abnormality is chylomicron elevation (Fredrickson types I and V).

Effects on ability to drive and use machines: Studies to determine the effect of Aurora on the ability to drive and use machines have not been conducted. However, based on its pharmacodynamics properties, Aurora is unlikely to affect this ability. When driving vehicles or operating machines. It should be taken into account that dizziness may occur during treatment.

DRUG INTERACTIONS

Effect of co-administered medicinal products on rosuvastatin

Cyclosporine: During concomitant treatment with rosuvastatin and cyclosporine, rosuvastatin AUG values were on average 7 times higher than those observed in healthy volunteers. Rosuvastatin is contraindicated in patients receiving concomitant cyclosporine. Concomitant administration did not affect plasma concentrations of cyclosporine.

Protease Inhibitors: Protease inhibitor use may strongly increase rosuvastatin exposure. For instance, in a pharmacokinetic study, co-administration of 10 mg rosuvastatin and a combination product of two protease inhibitors (300 mg atazanavir / 100 mg ritonavir] in healthy volunteers was associated with an approximately three-fold and seven-fold increase in rosuvastatin AUC and Cmax respectively. The concomitant use of rosuvastatin and some protease inhibitor combinations may be considered after careful consideration of rosuvastatin dose adjustments based on the expected increase in rosuvastatin exposure.

Gemfibrozil and other lipid-lowering products: Concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin Cmax and AUC. Based on data from specific interaction studies no pharmacokinetic relevant interaction with fenofibrate is expected, however a pharmacodynamics interaction may occur. Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (> or equal to lg/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. The 40 mg dose is contraindicated with concomitant use of a fibrate. These patients should also start with the 5 mg dose.

Ezetimibe: Concomitant use of 10 mg rosuvastatin and 10 mg ezetimibe resulted in a 1.2-fold increase in AUC of rosuvastatin in hypercholesterolaemic subjects. A pharmacodynamics interaction, in terms of adverse effects, between rosuvastatin and ezetimibe cannot be ruled out.

Antacid: 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.

Erythromycin: Concomitant use of rosuvastatin and erythromycin resulted in a 20% decrease in AUC and a 30% decrease in Cmax of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Cytochrome P450 enzymes: Rosuvastatin is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes. In addition, rosuvastatin is a poor substrate for these isoenzymes. Therefore, drug interactions resulting from cytochrome P450-mediated metabolism are not expected. No clinically relevant interactions have been observed between rosuvastatin and either fluconazole (an inhibitor of CYP2C9 and CYP3A4) or ketoconazole (an inhibitor of CYP2A6 and CYP3A4).

Effect of rosuvastatin on co-administered medicinal products

Vitamin K antagonists: As with other HMG-CoA reductase inhibitors, the initiation of treatment or dosage up-tit ration of rosuvastatin in patients treated concomitantly with vitamin K antagonists (e.g. warfarin or another coumarin anticoagulant) may result in an increase in International Normalized Ratio (INR). Discontinuation or down-titration of rosuvastatin may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.

Oral contraceptive/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.

Digoxin: Based on data from specific interaction studies no clinically relevant interaction with digoxin is expected.

Fusidic Acid: Interaction studies with rosuvastatin and fusidic acid have not been conducted. The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic add with statins. If treatment with systemic fusidic acid is necessary, rosuvastatin treatment should be discontinued throughout the duration of the fusidic add treatment.

HOW SUPPLIED

Aurora 5 mg Tablets:	Pack of 10 Tablets
Aurora 10 mg Tablets:	Pack of 10 Tablets
Aurora 20 mg Tablets:	Pack of 10 Tablets

STORAGE

Do not store above 30°C.
The expiration date refers to the product correctly stored at the required condition.

INSTRUCTIONS

Keep away from moisture, light and reach of children.
To be sold on the prescription of a registered medical practitioner only.

Please read the contents cautiously before use.
This package insert is regularly and timely updated.

Manufactured by:
FEROZSONS LABORATORIES LIMITED
P. O. Ferozsons, Nowshera-Pakistan
Mfg. Lic. No. 000038