

1.6.3 Patient Information Leaflet (PIL)

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<div style="text-align: center;">  </div> <p>COMPOSITION: Crestat Tablet 5mg: Each film-coated tablet contains: Rosuvastatin Calcium (Manufacturer's Specification) equivalent to Rosuvastatin..... 5 mg (CCL Pharmaceuticals Specifications)</p> <p>Crestat Tablet 10 mg: Each film-coated tablet contains: Rosuvastatin Calcium (Manufacturer's Specification) equivalent to Rosuvastatin..... 10 mg (CCL Pharmaceuticals Specifications)</p> <p>Crestat Tablet 20 mg: Each film-coated tablet contains: Rosuvastatin Calcium (Manufacturer's Specification) equivalent to Rosuvastatin..... 20 mg (CCL Pharmaceuticals Specifications)</p> <p>DESCRIPTION: Crestat (Rosuvastatin) is a synthetic lipid-lowering agent. The empirical formula for Rosuvastatin calcium is $C_{20}H_{26}F_2N_2O_5$, its molecular weight is 1001.14</p> <p>CLINICAL PHARMACOLOGY: Mechanism of Action: Crestat (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 of cholesterol.</p> <p>Pharmacokinetics: Absorption: In clinical pharmacology studies in man, peak plasma concentrations of Crestat (Rosuvastatin) were reached 3-5 hours following oral dosing. The absolute bioavailability of Rosuvastatin is approximately 20%.</p> <p>Distribution: Mean volume of distribution at steady-state of Crestat (Rosuvastatin) is approximately 124 liters. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.</p> <p>Metabolism: Crestat (Rosuvastatin) is not extensively metabolized; approximately 10% of a radio labeled dose is recovered as metabolite. The major metabolite is N-desmethyl Rosuvastatin which is formed principally by cytochrome P450 3C3 and in vitro studies have demonstrated that N-desmethyl Rosuvastatin has approximately one sixth to one-half the HMG-CoA reductase inhibitory activity of Rosuvastatin. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by Rosuvastatin.</p> <p>Excretion: Crestat (Rosuvastatin) and its metabolites are primarily excreted in the feces (90%). The elimination half-life (t_{1/2}) of Rosuvastatin is approximately 19 hours.</p> <p>Special Populations: Gender: There were no differences in plasma concentrations of Rosuvastatin between men and women.</p> <p>Geriatric: There were no differences in plasma concentrations of Rosuvastatin between the non elderly and elderly subjects (age > 65 years).</p> <p>Pediatric: In a pharmacokinetic study, 18 patients (9 boys and 9 girls) 10 to 17 years of age with heterozygous FH received single and multiple oral doses of Rosuvastatin. Both C_{max} and AUC of Rosuvastatin were similar to values obtained in adult subjects administered the same doses.</p> <p>Renal Insufficiency: Mild to moderate renal impairment (creatinine clearance < 30 ml/min/1.73 m²) had no influence on plasma concentrations of Rosuvastatin when oral doses of 20 mg Rosuvastatin were administered for 14 days. 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 m²) compared with healthy subjects (CL_{cr} > 80 ml/min/1.73 m²).</p> <p>Hepatic Impairment: Steady state plasma concentrations of Rosuvastatin in patients on chronic hemodialysis were approximately 50% greater compared with healthy volunteer subjects with normal renal function.</p> <p>Hepatic Insufficiency: In patients with chronic alcohol liver disease, plasma concentrations of Rosuvastatin were markedly 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.</p> <p>INDICATIONS AND USAGE: Crestat (Rosuvastatin) is indicated:</p> <ul style="list-style-type: none"> As an adjunct to diet to reduce elevated total C, LDL-C, ApoB, non-HDL-C, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb). As an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV). To reduce LDL-C, total C and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable. <p>CONTRAINDICATIONS: Crestat (Rosuvastatin) is contraindicated in patients with a known hypersensitivity to any component of this product.</p> <p>Rosuvastatin is contraindicated in patients with active liver disease or with unexplained persistent elevations of serum transaminases.</p> <p>Pregnancy and Lactation: Rosuvastatin should be administered to women of child bearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking this drug, therapy should be discontinued immediately and the patient apprised of the potential hazard to the fetus.</p> <p>DOSE AND ADMINISTRATION: Crestat (Rosuvastatin) can be administered as a single dose at any time of day, with or without food (hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb)). The dose range for Crestat (Rosuvastatin) is 5-40 mg once daily. Therapy with Crestat (Rosuvastatin) should be individualized according to goal of therapy and response. The usual recommended starting dose of Crestat (Rosuvastatin) is 10 mg once daily. However, initiation of therapy with 5 mg once daily may be considered for patients requiring less aggressive LDL-C reductions, who have predisposing factors for myopathy and/or as noted below for special populations such as patients taking cyclosporine. Asian patients, and patients with severe renal insufficiency. For patients with marked hypercholesterolemia (LDL-C > 190 mg/dL) and aggressive lipotargets, a 20 mg starting dose may be considered. After initiation and/or upon titration of Crestat (Rosuvastatin), lipid levels should be analyzed within 2-4 weeks and dosage adjusted accordingly.</p> <p>The 40 mg dose of Rosuvastatin is reserved only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose of Rosuvastatin once daily. When initiating stable therapy or switching from another stable therapy, the appropriate Rosuvastatin starting dose should first be utilized, and only then titrated according to the patient's individualized goal of therapy.</p> <p>Homozygous Familial Hypercholesterolemia: The recommended starting dose of Crestat (Rosuvastatin) is 20 mg once daily in patients with homozygous FH. The maximum recommended daily dose is 40 mg. Crestat (Rosuvastatin) should be used in these patients as an adjunct to other lipid lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable. Response to therapy should be estimated from pre-apheresis LDL-C levels.</p> <p>Dosage in Asian Patients: Initiation of Crestat (Rosuvastatin) therapy with 5 mg once daily should be considered for Asian patients. The potential for increased systemic exposure relative to Caucasians is relevant when considering escalation of dose in cases where hypercholesterolemia is not adequately controlled at doses of 5, 10, or 20 mg once daily.</p> <p>Dosage in Patients Taking Cyclosporine: In patients taking cyclosporine, therapy should be limited to Crestat (Rosuvastatin) 5 mg once daily.</p>	<p>Concomitant Lipid-Lowering Therapy: The effect of Crestat (Rosuvastatin) on LDL-C and total-C may be enhanced when used in combination with a bile acid binding resin. If Crestat (Rosuvastatin) is used in combination with gemfibrozil, the dose of Crestat (Rosuvastatin) should be limited to 10 mg once daily.</p> <p>Usage in Patients With Renal Insufficiency: No modification of dosage is necessary for patients with mild to moderate renal insufficiency. For patients with severe renal impairment (CL_{cr} < 30 ml/min/1.73 m²) nil or minimal dosages, dosing of Crestat (Rosuvastatin) should be started at 5 mg once daily and not to exceed 10 mg once daily.</p> <p>ADVERSE REACTIONS: Rosuvastatin is generally well tolerated. Adverse reactions have usually been mild and transient. The most frequent adverse events thought to be related to Rosuvastatin were myalgia, constipation, arthralgia, abdominal pain and rashes.</p> <p>Body as a Whole: Abdominal pain, chest pain, infection, pain, joint pain, and neck pain.</p> <p>Cardiovascular System: Hypertension, angina pectoris, vasodilatation, and palpitation.</p> <p>Digestive System: Constipation, gastroenteritis, vomiting, flatulence, periodontal abscess, and gastritis.</p> <p>Endocrine: Diabetes mellitus.</p> <p>Hemic and Lymphatic System: Anemia and ecchymosis.</p> <p>Metabolic and Nutritional Disorders: Peripheral edema.</p> <p>Musculoskeletal System: Arthritis, arthralgia, and pathological fracture.</p> <p>Nervous System: Dizziness, somnolence, hypertension, paresthesia, depression, ataxia, vertigo and neuralgia.</p> <p>Respiratory System: Sinusitis, cough increased, dyspnea, pneumonia and asthma.</p> <p>Skin and Appendages: Rash and pruritus.</p> <p>DRUG-DRUG INTERACTIONS: CYP 3A4: Rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent. This has been confirmed in studies with known cytochrome P450 3A4 inhibitors (ketorolac, erythromycin, itraconazole).</p> <p>Erythromycin: Co-administration of erythromycin (500 mg four times daily for 7 days) with Rosuvastatin (40 mg) resulted in a decrease in plasma concentrations of Rosuvastatin by 20% and 31%, respectively. These reductions are not considered clinically significant.</p> <p>Cyclosporine: Co-administration of cyclosporine with Rosuvastatin resulted in no significant changes in cyclosporine.</p> <p>Warfarin: Co-administration of warfarin (20 mg) with Rosuvastatin (40 mg) did not change warfarin plasma concentrations but increased the International Normalized Ratio (INR).</p> <p>Digoxin: Co-administration of digoxin (0.5 mg) with Rosuvastatin (40 mg) resulted in no change to digoxin plasma concentrations.</p> <p>Fenofibrate: Co-administration of fenofibrate (67 mg three times daily) with Rosuvastatin (10 mg) resulted in no significant changes in plasma concentrations of Rosuvastatin or fenofibrate.</p> <p>Alcohol: Co-administration of an antacid (aluminum and magnesium hydroxide combination) with Rosuvastatin (40 mg) resulted in a decrease in plasma concentrations of Rosuvastatin by 54%. However, when the antacid was given 2 hours after Rosuvastatin, there were no clinically significant changes in plasma concentrations of Rosuvastatin.</p> <p>Oral Contraceptives: Co-administration of oral contraceptives (ethinyl estradiol and norgestrel) with Rosuvastatin resulted in an increase in plasma concentrations of ethinyl estradiol and norgestrel by 26% and 34%, respectively.</p> <p>WARNING:</p> <ul style="list-style-type: none"> Rosuvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Rosuvastatin should be prescribed with caution in patients with predisposing factors for myopathy, such as, renal impairment. Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by myalgia or fever. Rosuvastatin therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected. <p>Pregnancy: Pregnancy Category E: Rosuvastatin is contraindicated in women who are or may become pregnant.</p> <p>Nursing Mothers: It is not known whether Rosuvastatin is excreted in human milk. The decision to discontinue nursing or administration of Rosuvastatin should be made taking into account the importance of the drug to the lactating woman.</p> <p>Pediatric Use: The safety and effectiveness in pediatric patients have not been established. Treatment experience with Rosuvastatin in a pediatric population is limited to 8 patients with homozygous FH. None of these patients was below 6 years of age.</p> <p>DRUG INTERACTIONS: Cyclosporine: When Rosuvastatin 10mg was coadministered with cyclosporine in cardiac transplant patients, Rosuvastatin mean C_{max} and mean AUC were increased 11-fold and 7-fold, respectively, compared with healthy volunteers. These increases require special consideration in the dosing of Rosuvastatin to patients taking concomitant cyclosporine.</p> <p>Warfarin: Co-administration of Rosuvastatin to patients on stable warfarin therapy resulted in clinically significant rises in INR (4.4, baseline 2.3). In patients taking coumatin anticoagulants and Rosuvastatin concomitantly, INR should be determined before starting Rosuvastatin.</p> <p>Gemfibrozil: Co-administration of a single Rosuvastatin dose to healthy volunteers on gemfibrozil (600 mg twice daily) resulted in a 2.2- and 1.8-fold, respectively, increase in mean C_{max} and mean AUC of Rosuvastatin.</p> <p>OVERDOSAGE: There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Hemodialysis does not significantly enhance clearance of Rosuvastatin.</p> <p>INSTRUCTIONS:</p> <ul style="list-style-type: none"> Store below 30°C. Protect from heat, sunlight and moisture. Keep out of the reach of children. Take only on the prescription of a registered medical practitioner only. <p>PRESENTATION:</p> <table border="0"> <tr> <td>Crestat Tablet 5mg</td> <td>:</td> <td>Pack of 1 X 10 Tablets.</td> </tr> <tr> <td>Crestat Tablet 5mg</td> <td>:</td> <td>Pack of 3 X 10 Tablets.</td> </tr> <tr> <td>Crestat Tablet 10mg</td> <td>:</td> <td>Pack of 1 X 10 Tablets.</td> </tr> <tr> <td>Crestat Tablet 10mg</td> <td>:</td> <td>Pack of 3 X 10 Tablets.</td> </tr> <tr> <td>Crestat Tablet 20mg</td> <td>:</td> <td>Pack of 1 X 10 Tablets.</td> </tr> <tr> <td>Crestat Tablet 20mg</td> <td>:</td> <td>Pack of 3 X 10 Tablets.</td> </tr> </table> <p>FOR FURTHER INFORMATION, PLEASE CONTACT:</p> <p style="text-align: center;">  Manufactured by: CCL Pharmaceuticals (Pvt.) Ltd. 62 Industrial Estate, Nur Lahore, Lahore, Pakistan. </p> <p style="text-align: right;">2580 2581 0049-551-0000-0000</p>	Crestat Tablet 5mg	:	Pack of 1 X 10 Tablets.	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