1.5.3 Patient Information Leaflet (PIL)

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Crestat

Rosuvastatin

Tablet

COMPOSITION:

Crestat Tablet 5 mg:
Each film coated tablet contains
Rosuvastatin Calcium (Manufacturer's Specs.)
equivalent to Rosuvastatin..... 5 mg
(CCL Pharmaceuticals Specifications)

Crestat Tablet 10 mg:
Each film coated tablet contains
Rosuvastatin Calcium (Manufacturer's Specs.)
equivalent to Rosuvastatin..... 10 mg
(CCL Pharmaceuticals Specifications)

Crestat Tablet 20 mg:
Each film coated tablet contains
Rosuvastatin Calcium (Manufacturer's Specs.)
equivalent to Rosuvastatin..... 20 mg
(CCL Pharmaceuticals Specifications)

DESCRIPTION:

Crestat (Rosuvastatin) is a synthetic lipid-lowering agent. The empirical formula for **Rosuvastatin calcium** is $C_{22}H_{28}CaF_2N_6O_6S_2$, its molecular weight is 1001.14.

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.

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%.
Distribution:
Mean volume of distribution at steady-state of **Crestat (Rosuvastatin)** is approximately 134 liters. **Rosuvastatin** is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.
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 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 **Rosuvastatin**. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by **Rosuvastatin.**
Excretion:
Crestat (Rosuvastatin) and its metabolites are primarily excreted in the feaces (90%). The elimination half-life ($t^{1/2}$) of **Rosuvastatin** is approximately 19 hours.
Special Populations:
Gender:
There were no differences in plasma concentrations of **Rosuvastatin** between men and women.
Geriatric:
There were no differences in plasma concentrations of **Rosuvastatin** between the non elderly and elderly populations (age > 65 years).
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 observed in adult subjects administered the same doses.
Renal Insufficiency:
Mild to moderate renal impairment (creatinine clearance >30 ml/min/1.73 m^2) 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 (CLcr <30 ml/min/1.73 m^2) compared with healthy subjects (CLcr >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 Insufficiency:
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.

INDICATIONS AND USAGE:
Crestat (Rosuvastatin) is indicated:

- 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.

CONTRAINDICATIONS:
Crestat (Rosuvastatin) is contraindicated in patients with a known hypersensitivity to any component of this product.
Rosuvastatin is contraindicated in patients with active liver disease or with unexplained persistent elevations of serum transaminases.
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 appraised of the potential hazard to the fetus.

DOSAGE 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 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 lipid targets, 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.
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 statin therapy or switching from another statin therapy, the approximate **Rosuvastatin** starting dose should first be utilized, and only then titrated according to the patient's individualized goal of therapy.
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.
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 exposures 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.
Dosage in Patients Taking Cyclosporine:
In patients taking cyclosporine, therapy should be limited to **Crestat (Rosuvastatin)** 5 mg once daily.

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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.
Dosage 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 (CLcr <30 ml/min/1.73 m^2) not on hemodialysis, dosing of **Crestat (Rosuvastatin)** should be started on 5 mg once daily and not to exceed 10 mg once daily.

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, asthenia, abdominal pain and nausea.
Body as a Whole: Abdominal pain, chest pain, infection, pain, pelvic pain, and neck pain.
Cardiovascular System: Hypertension, angina pectoris, vasodilatation, and palpitation.
Digestive System: Constipation, gastroenteritis, vomiting, flatulence, periodontal abscess, and gastritis.
Endocrine: Diabetes mellitus.
Hemic and Lymphatic System: Anemia and ecchymosis.
Metabolic and Nutritional Disorders: Peripheral edema.
Musculoskeletal System: Arthritis, arthralgia, and pathological fracture.
Nervous System: Dizziness, insomnia, hypertonia, paresthesia, depression, anxiety, vertigo and neuralgia.
Respiratory System: Bronchitis, cough increased, dyspnea, pneumonia and asthma.
Skin and Appendages: Rash and pruritus.

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 (ketoconazole, erythromycin, itraconazole).
Erythromycin: Co-administration of erythromycin (500 mg four times daily for 7 days) with **Rosuvastatin** (80 mg) decreased AUC and C_{max} of **Rosuvastatin** by 20% and 31%, respectively. These reductions are not considered clinically significant.
Cyclosporine: Co-administration of cyclosporine with **Rosuvastatin** resulted in no significant changes in cyclosporine.
Warfarin: Co-administration of warfarin (25 mg) with **Rosuvastatin** (40 mg) did not change warfarin plasma concentrations but increased the International Normalized Ratio (INR).
Digoxin: Co-administration of digoxin (0.5 mg) with **Rosuvastatin** (40 mg) resulted in no change to digoxin plasma concentrations.
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.
Antacid: 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**.
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.

WARNINGS:

- **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 malaise or fever.
- **Rosuvastatin** therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected.

Pregnancy:
Pregnancy Category X:
Rosuvastatin is contraindicated in women who are or may become pregnant.
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.
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 8 years of age.

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.
Warfarin: Coadministration of **Rosuvastatin** to patients on stable warfarin therapy resulted in clinically significant rises in INR (>4, baseline 2-3). In patients taking coumarin anticoagulants and **Rosuvastatin** concomitantly, INR should be determined before starting **Rosuvastatin.**
Gemfibrozil: Coadministration of a single **Rosuvastatin** dose to healthy volunteers on gemfibrozil (600 mg twice daily) resulted in a 2.2- and 1.9-fold, respectively, increase in mean C_{max} and mean AUC of **Rosuvastatin.**

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.**

INSTRUCTIONS:
- Store below 30°C.
- Protect from heat, sunlight and moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:

Crestat Tablet 5 mg	:	Pack of 1X10 tablets.
Crestat Tablet 5 mg	:	Pack of 3X10 tablets.
Crestat Tablet 10 mg	:	Pack of 1X10 tablets.
Crestat Tablet 10 mg	:	Pack of 3X10 tablets.
Crestat Tablet 20 mg	:	Pack of 1X10 tablets.
Crestat Tablet 20 mg	:	Pack of 3X10 tablets.

FOR FURTHER INFORMATION PLEASE CONTACT

CCL

Manufactured by:
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