130mm x 180mm

Front

Crestat®
(Rosuvastatin)
Tablet

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COMPOSITION:
Crestat Tablet 5 mg:
Each film coated tablet contains:
Rosuvastatin Calcium equivalent to
Rosuvastatin ..... 5 mg.

Product Specs.: CCL Pharmaceuticals

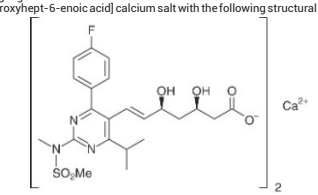
Crestat Tablet 10 mg:
Each film coated tablet contains:
Rosuvastatin Calcium equivalent to
Rosuvastatin ..... 10 mg.

Product Specs.: CCL Pharmaceuticals

Crestat Tablet 20 mg:
Each film coated tablet contains:
Rosuvastatin Calcium equivalent to
Rosuvastatin ..... 20 mg.

Product Specs.: CCL Pharmaceuticals

DESCRIPTION:
CRESTAT (rosuvastatin calcium) is a synthetic lipid-lowering agent for oral administration. The chemical name for rosuvastatin calcium is bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2 [methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt with the following structural formula:



The empirical formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2Ca$ 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.
CLINICAL PHARMACOLOGY:
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 of cholesterol. Rosuvastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.
Pharmacokinetics:
Absorption: Peak plasma concentrations of rosuvastatin were reached 3 to 5 hours following oral dosing. Both Cmax and AUC increased in approximate proportion to Rosuvastatin dose. The absolute bioavailability of rosuvastatin is approximately 20%.
Administration with food did not affect the AUC of rosuvastatin. The AUC of rosuvastatin does not differ following evening or morning drug administration.
Distribution: 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.
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 P450/2C9.
Elimination: Following oral administration, rosuvastatin and its metabolites are primarily excreted in the feces
(90%). The elimination half-life (t1/2) 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.
Pharmacokinetics in Special Populations :
Race: Pharmacokinetic studies have demonstrated an approximate 2-fold elevation in median exposure (AUC and Cmax) in Asian subjects when compared with a Caucasian control group.
Gender: There were no differences in plasma concentrations of rosuvastatin between men and women.
Pediatric: In a population pharmacokinetic analysis of pediatric trials involving patients with heterozygous familial hypercholesterolemia 10 to 17 years of age and 8 to 17 years of age, respectively, rosuvastatin exposure appeared comparable to or lower than rosuvastatin exposure in adult patients.
Geriatric: There were no differences in plasma concentrations of rosuvastatin between the no- elderly and elderly populations (age ≥ 65 years).
Renal Impairment: Mild to moderate renal impairment (CLcr ≥ 30 mL/min/1.73 m²) 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 (CLcr <30 mL/min/1.73 m²) .
Hepatic Impairment: In patients with chronic alcohol liver disease, plasma concentrations of rosuvastatin were modestly increased. In patients with Child-Pugh A disease, Cmax and AUC were increased by 60% and 5%, respectively, as compared with patients with normal liver function. In patients with Child-Pugh B disease, Cmax and AUC were increased 100% and 21%, respectively, compared with patients with normal liver function.

INDICATIONS AND USAGE:
- ***Hyperlipidemia and Mixed Dyslipidemia:***
  CRESTAT is indicated as adjunctive therapy to diet to reduce elevated Total-C, LDL-C, ApoB, nonHDL-C, 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 non pharmacological interventions alone has been inadequate.
- ***Pediatric Patients with Familial Hypercholesterolemia:***

CRESTAT is indicated as an adjunct to diet to:
- Reduce Total-C, LDL-C and ApoB levels in children and adolescents 8 to17 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: CRESTAT is indicated as adjunctive therapy to diet for the treatment of adult patients with hypertriglyceridemia.
Primary Dysbetalipoproteinemia (Type III Hyperlipoproteinemia): CRESTAT is indicated as an adjunct to diet for the treatment of adult patients with primary dysbetalipoproteinemia (Type III Hyperlipoproteinemia).
Adult Patients with Homozygous Familial Hypercholesterolemia: CRESTAT 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: CRESTAT 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 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 HDL-C, smoking, or a family history of premature coronary heart disease, CRESTAT is indicated to:
- Rreduce the risk of stroke
- Reduce the risk of myocardial infarction
- Reduce the risk of arterial revascularization procedures

Limitations of Use:
Rosuvastatin has not been studied in Fredrickson Type I and V dyslipidemias.

DOSAGE AND ADMINISTRATION:
General Dosing Information:
- The dose range for CRESTAT in adults is 5 to 20 mg orally once daily.

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- The usual starting dose is 10 to 20 mg once daily.
- The usual starting dose in adult patients with homozygous familial hypercholesterolemia is 20 mg once daily.
- The maximum CRESTAT dose of 40 mg should be used only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose.

CRESTAT can be administered as a single dose at any time of day, with or without food. The tablet should be swallowed whole. After initiation or upon titration of CRESTAT, lipid levels should be analyzed within 2 to 4 weeks and the dosage adjusted accordingly. In heterozygous familial hypercholesterolemia, the recommended dose range is 5 to 10 mg orally once daily in patients 8 to less than 10 years of age, and 5 to 20 mg orally once daily in patients 10 to 17 years of age. In homozygous familial hypercholesterolemia, the recommended dose is 20 mg orally once daily in patients 7 to 17 years of age.

DOSE MODIFICATION RECOMMENDATIONS:
Dosing in Asian Patients: In Asian patients, consider initiation of CRESTAT 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.
CONTRAINDICATIONS:
CRESTAT is contraindicated in the following condition:
- Patients with a known hypersensitivity to any component of this product. Hypersensitivity reactions including rash, pruritus, urticaria, and angioedema have been reported with rosuvastatin.
- Patients with active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels
- Pregnancy

Lactation: Because statins have the potential for serious adverse reactions in nursing infants, women who require CRESTAT treatment should not breastfeed their infants.

WARNINGS AND PRECAUTIONS:
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). Rosuvastatin should be prescribed with caution in patients with predisposing factors for myopathy (e.g., age ≥ 65 years, inadequately treated hypothyroidism, renal impairment). Rosuvastatin therapy should be discontinued if markedly elevated creatine kinase levels occur or myopathy is diagnosed or suspected. Rosuvastatin 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. All patients should be advised to promptly report to their physician unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing Rosuvastatin.
Liver Enzyme Abnormalities: It is recommended that liver enzyme tests be performed before the initiation of Rosuvastatin, and if signs or symptoms of liver injury occur.
Increases in serum transaminases [AST (SGOT) or ALT (SGPT)] have been reported with HMG-CoA reductase inhibitors, including Rosuvastatin. CRESTAT should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of chronic liver disease. Active liver disease, which may include unexplained persistent transaminase elevations, is a contraindication to the use of CRESTAT.
Concomitant Coumarin Anticoagulants: Caution should be exercised when anticoagulants are given in conjunction with CRESTAT because of its potentiation of the effect of coumarin-type anticoagulants in prolonging the prothrombin time/INR. In patients taking coumarin anticoagulants and CRESTAT concomitantly, INR should be determined before starting CRESTAT and frequently enough during early therapy to ensure that no significant alteration of INR occur
Proteinuria and Hematuria: Dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin treated patients taking rosuvastatin 40 mg, when compared to lower doses of CRESTAT or comparator HMG-CoA reductase inhibitors, though it was generally transient and was not associated with worsening renal function. A dose reduction should be considered for patients on rosuvaststin therapy with unexplained persistent proteinuria and/or hematuria during routine urinalysis testing.
Endocrine Effects: Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including Rosuvastatin. Caution should be exercised if CRESTAT is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

DRUG INTERACTIONS:
Cyclosporine: Cyclosporine increased rosuvastatin exposure (AUC) 7-fold. Therefore, in patients taking cyclosporine, the dose of CRESTAT should not exceed 5 mg once daily.
Gemfibrozil: Gemfibrozil significantly increased rosuvastatin exposure. Due to an observed increased risk of myopathy/rhabdomyolysis, combination therapy with CRESTAT and gemfibrozil should be avoided. If used together, the dose of CRESTAT should not exceed 10 mg once daily.
Protease Inhibitors: Coadministration of rosuvastatin with certain protease inhibitors has differing effects on rosuvastatin exposure. Caution should be exercised when rosuvastatin is coadministered with protease inhibitors.
Coumarin Anticoagulants: CRESTAT significantly increased INR in patients receiving coumarin anticoagulants. Therefore, caution should be exercised when coumarin anticoagulants are given in conjunction with CRESTAT. In patients taking coumarin anticoagulants and CRESTAT concomitantly, INR should be determined before starting CRESTAT and frequently enough during early therapy to ensure that no significant alteration of INR occurs.
Niacin: The risk of skeletal muscle effects may be enhanced when CRESTAT is used in combination with lipid-modifying doses (≥ 1 g/day) of niacin; caution should be used when prescribing with CRESTAT.
Fenofibrate: When CRESTAT was coadministered 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 fenofibrates, caution should be used when prescribing fenofibrates with CRESTAT.
Colchicine: Cases of myopathy, including rhabdomyolysis, have been reported with HMG-CoA reductase inhibitors, including rosuvastatin, coadministered with colchicine, and caution should be exercised when prescribing CRESTAT with colchicine.

USE IN SPECIFIC POPULATIONS:
Pregnancy: CRESTAT is contraindicated for use in pregnant women since safety in pregnant women has not been established and there is no apparent benefit to therapy with Rosuvastatin during pregnancy.
Nursing Mothers: Rosuvastatin use is contraindicated during Lactation. CRESTAT is present in human milk. Because of the potential for serious adverse reactions in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with CRESTAT.
Females and Males of Reproductive Potential:
Contraception: CRESTAT may cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with CRESTAT.
Pediatric Use: The same warnings and precautions for adults should be considered for children and adolescents. Adolescent females should be counseled on appropriate contraceptive methods while on CRESTAT therapy.
Geriatric Use: No overall differences in safety or effectiveness were observed between the elderly and younger patients. Elderly patients are at higher risk of myopathy and CRESTAT should be prescribed with caution in the elderly.
Patients with Renal Impairment: Rosuvastatin exposure is not influenced by mild to moderate renal impairment (CLcr ≥ 30 mL/min/1.73 m²). Exposure to rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment (CLcr <30 mL/min/1.73 m²) who are not receiving hemodialysis and dose adjustment is required. Exposure to rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment (CLcr <30 mL/min/1.73 m²) who are not receiving hemodialysis and dose adjustment is required.
Patients with Hepatic Impairment: CRESTAT 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; CRESTAT should be used with caution in these patients.
Asian Patients: An approximate 2-fold increase in median exposure to rosuvastatin in Asian subjects when compared with Caucasian controls. CRESTAT dosage should be adjusted in Asian patients.

ADVERSE REACTIONS:
The following serious adverse reactions are discussed in greater detail in other sections of the label *Specific:*
- Rhabdomyolysis with myoglobinuria and acute renal failure and myopathy (including myositis)
- Liver enzyme abnormalities

Common adverse reactions:
- The most common adverse reactions that led to treatment discontinuation during trials were:
- Myalgia
- Abdominal pain
- Nausea
- Headache
- Asthenia

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 & 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 1 x 10 tablets.
Crestat Tablet 10 mg	:	Pack of 1 x 10 tablets.
Crestat Tablet 20 mg	:	Pack of 1 x 10 tablets.

ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATION PLEASE CONTACT:

Manufactured by:
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