## 1.6 Product Information

### 1.6.1 Prescribing Information

**(SUMMARY OF PRODUCT CHARACTERISTICS)**

**Name of the Finished Pharmaceutical Product**

**Product name**

Crestat Tablet 10mg

**Strength**

10mg

**Pharmaceutical form**

Film coated tablet

**Qualitative and Quantitative Composition**

**Qualitative Declaration**

Rosuvastatin calcium

**Quantitative Declaration**

Each film coated tablet contains:
Rosuvastatin (as calcium) ……..10mg

**Pharmaceutical Form**

Light blue round biconvex film coated tablet.

**Clinical Particulars:**

**Therapeutic Indications**

1. As an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and non familial) and mixed dyslipidemia (Fredrickson Type IIa and IIb).

2. As an adjunct to diet for the treatment patients with elevated serum TG levels Fredrickson Type IV).
3. 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 aphresis) or if such treatments are unavailable.

**Posology and Method of Administration**

Crestat (Rosuvastatin) can be administered as a single dose at any time of day, with or without food. Hypercholesterolemia (Heterozygous Familial and Non familial) and Mixed Dyslipidemia (Fredrickson Type IIa and llb)

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 10 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 t6 therapy should be estimated from pre-apheresis LDL-C levels.

**Dosage in Asian Patients**
Initiation of Crestat (Rosuvastatin) therapy with 10mg 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, 1 0 or 20mg once daily.

**Dosage in Patients Taking Cyclosporine**
In patients taking cyclosporine, therapy should be limited to Crestat (Rosuvastatin) 10mg once daily.

**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 mllmin/1.73 m') not on hemodialysis,

dosing of Crestat (Rosuvastatin) should be started at 10 mg once daily and not to exceed 10 mg. once daily.

**Method of Administration**

Oral

**Contra Indications**

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 elevation of serum transaminasees.

Rosuvastatin should be administered to women of child bearing age only when such patient 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.

**Special Warning and Precautions for Use**

**WARNINGS:**

**Liver Enzymes**
Rosuvastatin should be used with caution in patients who consume substantial quantities, of alcohol and/or have a history of liver disease.

**Myopathy / Rhabdomyolysis**
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.

**PRECAUTIONS:**

**Drug Interactions**

**Cyclosporine:**
When Rosuvastatin 10mg was co-administered with cyclosporine in cardiac transplant patients, Rosuvastatin mean Cmax 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:**
Co-administration 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:**
Co administration 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 Cm"x and mean AUC of Rosuvastatin.

**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 women.

**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.

**Additional Information on Special Populations**

Not Applicable

**UNDESIRABLE EFFECTS:**
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, natulence, 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

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

**OVERDOSES**:

There is no specific treatment in the event of overdose. In the event 6f overdose, the patient should. Is treated symptomatically and supportive .measures instituted as required?
Hemodialysis does not significantly enhance clearance of Rosuvastatin.

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamic properties**:

**ATC classification**

Pharmacotherapeutic group: HMG-CoA reductase inhibitors

**ATC code**: C10A A07

**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.

**Pharmacodynamic effects**
Crestat reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I (see Table 1). Crestat also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

**Dose response in patients with primary hypercholesterolaemia (type IIa and IIb) (adjusted mean percent change from baseline)**

| Dose | N | LDL-C | Total-C | HDL-C | TG | nonHDL-C | ApoB | ApoA-I |
|---|---|---|---|---|---|---|---|---|
| Placebo | 13 | -7 | -5 | 3 | -3 | -7 | -3 | 0 |
| 5 | 17 | -45 | -33 | 13 | -35 | -44 | -38 | 4 |
| 10 | 17 | -52 | -36 | 14 | -10 | -48 | -42 | 4 |
| 20 | 17 | -55 | -40 | 8 | -23 | -51 | -46 | 5 |
| 40 | 18 | -63 | -46 | 10 | -28 | -60 | -54 | 0 |

A therapeutic effect is obtained within 1 week following treatment initiation and 90% of maximum response is achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

**Clinical efficacy**
Crestat is effective in adults with hypercholesterolaemia, with and without hypertriglyceridaemia, regardless of race, sex, or age and in special populations such as diabetics, or patients with familial hypercholesterolaemia. ]

From pooled phase III data, Crestat has been shown to be effective at treating the majority of patients with type IIa and IIb hypercholesterolaemia (mean baseline LDL- C about 4.8 mmol/l) to recognised European Atherosclerosis Society (EAS; 1998) guideline targets; about 80% of patients treated with 10 mg reached the EAS targets for LDL-C levels (<3 mmol/l).

In a large study, 435 patients with heterozygous familial hypercholesterolaemia were given Crestat from 20 mg to 80 mg in a force-titration design. All doses showed a beneficial effect on lipid parameters and treatment to target goals. Following titration to a daily dose of 40 mg (12 weeks of treatment), LDL-C was reduced by 53%. 33% of patients reached EAS guidelines for LDL-C levels (<3 mmol/l).

In a force-titration, open label trial, 42 patients with homozygous familial hypercholesterolaemia were evaluated for their response to Crestat 20 - 40 mg. In the overall population, the mean LDL-C reduction was 22%.

In clinical studies with a limited number of patients, Crestat has been shown to have additive efficacy in lowering triglycerides when used in combination with fenofibrate and in increasing HDL-C levels when used in combination with niacin.

In a multi-centre, double-blind, placebo-controlled clinical study (METEOR), 984 patients between 45 and 70 years of age and at low risk for coronary heart disease (defined as Framingham risk <10% over 10 years), with a mean LDL-C of 4.0 mmol/l (154.10 mg/dL), but with subclinical atherosclerosis (detected by Carotid Intima Media Thickness) were randomised to 40 mg Rosuvastatin once daily or placebo for 2 years. Rosuvastatin significantly slowed the rate of progression of the maximum CIMT for the 12 carotid artery sites compared to placebo by -0.0145 mm/year [95% confidence interval -0.0196, -

0.0093; p<0.0001]. The change from baseline was -0.0014 mm/year (-0.12%/year (non-significant)) for Rosuvastatin compared to a progression of +0.0131 mm/year (1.12%/year (p<0.0001)) for placebo. No direct correlation between CIMT decrease and reduction of the risk of cardiovascular events has yet been demonstrated. The population studied in METEOR is low risk for coronary heart disease and does not represent the target population of Crestat 40mg. The 40mg dose should only be prescribed in patients with severe hypercholesterolaemia at high cardiovascular risk.

In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, the effect of Rosuvastatin on the occurrence of major atherosclerotic cardiovascular disease events was assessed in 17,802 men ( ≥ 50 years) and women ( ≥ 60 years).

Study participants were randomly assigned to placebo (n=8901) or Rosuvastatin 20 mg once daily (n=8901) and were followed for a mean duration of 2 years.

LDL-cholesterol concentration was reduced by 45% (p<0.001) in the Rosuvastatin group compared to the placebo group.

In a post-hoc analysis of a high-risk subgroup of subjects with a baseline Framingham risk score>20% (1558 subjects) there was a significant reduction in the combined end- point of cardiovascular death, stroke and myocardial infarction (p=0.028) on Rosuvastatin treatment versus placebo. The absolute risk reduction in the event rate per 1000 patient-years was 8.8. Total mortality was unchanged in this high risk group (p=0.193). In a post-hoc analysis of a high-risk subgroup of subjects (9302 subjects total) with a baseline SCORE risk ≥ 5% (extrapolated to include subjects above 65 yrs) there was a significant reduction in the combined end-point of cardiovascular death, stroke and myocardial infarction (p=0.0003) on Rosuvastatin treatment versus placebo. The absolute risk reduction in the event rate was 5.1 per 1000 patient-years. Total mortality was unchanged in this high risk group (p=0.076).

In the JUPITER trial there were 6.6% of Rosuvastatin and 6.2% of placebo subjects who discontinued use of study medication due to an adverse event. The most common adverse events that led to treatment discontinuation were: myalgia (0.3% Rosuvastatin, 0.2% placebo), abdominal pain (0.03% Rosuvastatin, 0.02% placebo) and rash (0.02% Rosuvastatin, 0.03% placebo). The most common adverse events at a rate greater than or equal to placebo were urinary tract infection (8.7% Rosuvastatin, 8.6% placebo), nasopharyngitis (7.6% Rosuvastatin, 7.2% placebo), back pain (7.6% Rosuvastatin, 6.9% placebo) and myalgia (7.6% Rosuvastatin, 6.6% placebo).

**Paediatric population**

In a double-blind, randomized, multi-centre, placebo-controlled, 12-week study (n=176, 97 male and 79 female) followed by a 40-week (n=173, 96 male and 77 female), open-label, Rosuvastatin dose-titration phase, patients 10-17 years of age (Tanner stage II-V, females at least 1 year post-menarche) with heterozygous familial hypercholesterolaemia received Rosuvastatin 5, 10 or 20 mg or placebo daily for 12 weeks and then all received Rosuvastatin daily for 40 weeks. At study entry, approximately 30% of the patients were 10-13 years and approximately 17%, 18%, 40%, and 25% were Tanner stage II, III, IV, and V, respectively.

LDL-C was reduced 38.3%, 44.6%, and 50.0% by Rosuvastatin 5, 10 and 20 mg, respectively, compared to 0.7% for placebo.

At the end of the 40-week, open-label, titration to goal, dosing up to a maximum of 20 mg once daily, 70 of 173 patients (40.5%) had achieved the LDL-C goal of less than 2.8 mmol/l.

After 52 weeks of study treatment, no effect on growth, weight, BMI or sexual maturation was detected. The clinical trial experience in children and adolescent patients is limited and the long-term effects of Rosuvastatin (>1 year) on puberty are unknown. This trial (n=176) was not suited for comparison of rare adverse drug events.

**Pharmacokinetic properties:**

**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 II 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 reduetase 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 feces (90%). The elimination half life (t/z) 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 to17 years of age with heterozygous FH received single and multiple oral doses of Rosuvastatin. Both Cmax 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/1.73m$^2$) 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/I.73m$^2$) compared with healthy subjects (CLcr >80ml/min/1.73m$^2$).

**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, Cmax and AUG were increased by 60% and 5%, respectively, as compared with patients with normalliver funeti"n. In patients with Child-Pugh B disease, Cmax and AUC were increased 100% and 21 %, respectively, compared with patients with normal liver function.

## PHARMACEUTICAL PARTICULARS

### List of Excipients

**For Core**
- Magnesium Stearate
- Aerosil 200
- Avecil pH 102
- Croscarmellose Sodium
- Lactose DC

**For Film coating:**
- Opadry OY-C-7000 A (White)
- Color Brilliant Blue Lake
- Methanol
- Eudragit E 100
- Methylene Chloride
- Isopropyl Alcohol
- Polyethylene Glycol 6000

### Incompatibilities

Not applicable.

**Shelf-Life**

2 years

**Special Precautions for Storage**

- Stored below 30ºC.
- Protect from heat sunlight and moisture
- Keep away from heat, moisture, light and children

**Nature and Contents of Container**

3x10's tablets packed in Alu-Alu blister, in bleach board unit carton with leaflet.

**Special Precautions for Disposal and other Handling**

Not applicable

**Marketing Authorization Holder and Manufacturing Site Address**

| | |
|---|---|
| Name: | CCL Pharmaceuticals (Pvt.) Ltd. |
| Address: | 62-Industrial Estate, Kot Lakhpat, Lahore-54770, Pakistan. |
| Telephone: | +92-42-5114753 |
| Fax: | +92-42-35114382 |
| E-mail: | mail.ccl@cclpharma.com, |

**Marketing Authorization Number**

042691

**Date of First Authorization / Renewal of Authorization**

| | |
|---|---|
| Date of first authorization | 01-03-2006 |
| Date of second renewal | 01-03-2011 |
| Date of third renewal | 01-03-2016 |
| Date of last renewal | 01-03-2021 |
| Date of next renewal | 01-03-2026 |

**Date of Revision of the Text**

02-02-2026