The following serious adverse reactions have been reported very rarely:
- Rhabdomyolysis with myoglobinuria and acute renal failure and myopathy (including myositis).
- Liver enzyme abnormalities.

Other adverse reactions are abdominal pain, dizziness, hypersensitivity (including rash, pruritus, urticaria, and angioedema) and pancreatitis.

DRUG INTERACTIONS

Cyclosporine
Cyclosporine increased rosuvastatin exposure (AUC) 7-fold. Therefore, in patients taking cyclosporine, the dose of ROSTAT 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 ROSTAT and gemfibrozil should be avoided. If used together, the dose of ROSTAT should not exceed 10 mg once daily.

Protease Inhibitors
Co-administration of rosuvastatin with certain protease inhibitors has differing effects on rosuvastatin exposure. Simeprevir, which is a hepatitis C virus (HCV) protease inhibitor, or combinations of atazanavir / ritonavir or lopinavir / ritonavir, which are HIV-1 protease inhibitors, increase rosuvastatin exposure (AUC) up to threefold. For these protease inhibitors, the dose of ROSTAT should not exceed 10 mg once daily. The combinations of fosamprenavir / ritonavir or tipranavir / ritonavir, which are HIV-1 protease inhibitors, produce little or no change in rosuvastatin exposure. Caution should be exercised when rosuvastatin is co- administered with protease inhibitors.

Coumarin Anticoagulants
Rosuvastatin significantly increased INR in patients receiving coumarin anticoagulants. Therefore, caution should be exercised when coumarin anticoagulants are given in conjunction with ROSTAT.

Niacin
The risk of skeletal muscle effects may be enhanced when rosuvastatin is used in combination with lipid-modifying doses (≥1 g/day) of niacin; caution should be used when prescribing with ROSTAT.

Fenofibrate
When rosuvastatin was co-administered 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,

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.

STORAGE

Store below 30°C in a dry place, protect from light.
To be dispensed on the prescription of a registered medical practitioner only.
Keep out of the reach of children.

PRESENTATION

ROSTAT 5mg Tablets are supplied in Alu Alu Blister pack of 1 x 10's.
ROSTAT 10mg Tablets are supplied in Alu Alu Blister pack of 1 x 10's.
ROSTAT 20mg Tablets are supplied in Alu Alu Blister pack of 1 x 10's.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر خشک جگہ پر رکھیں، روشنی سے بچائیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔

Note: Product contains lactose. نوٹ: پروڈکٹ میں لیکٹوز شامل ہے۔

Manufactured by:

Platinum
Pharmaceuticals (Pvt.) Ltd.
A 20,North Western Industrial Zone,
Bin Qasim, Karachi-75020, Pakistan.

QARNo. AW22-1070

Mfg. Lic No. 000415

Rostat
(Rosuvastatin)

روسٹیٹ
(روسواسٹیٹن)

COMPOSITION

Rostat 5 mg Tablet	Rostat 10 mg Tablet	Rostat 20 mg Tablet
Each film coated tablet contains:	Each film coated tablet contains:	Each film coated tablet contains:
Rosuvastatin (As calcium) … 5 mg	Rosuvastatin (As calcium) ... 10 mg	Rosuvastatin (As calcium) ... 20 mg
Product Complies U.S.P. Specs	Product Complies U.S.P. Specs	Product Complies U.S.P. Specs

DESCRIPTION

ROSTAT (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.

CLINICAL PHARMACOLOGY

Mechanism of Action
ROSTAT 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. *In in vivo and in vitro studies*, 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
In clinical pharmacology studies in man, peak plasma concentrations of rosuvastatin were reached 3 to 5 hours following oral dosing. Both C_{max} and AUC increased in approximate proportion to ROSTAT dose. The absolute bioavailability of rosuvastatin is approximately 20%. Administration of ROSTAT 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, and in vitro studies have demonstrated that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of the parent compound. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by the parent compound.

Excretion
Following oral administration, rosuvastatin and its metabolites are primarily excreted in the feces (90%). The elimination half-life ($t_{1/2}$) of rosuvastatin is approximately 19 hours.

Specific Populations

Gender
There were no differences in plasma concentrations of rosuvastatin between men and women.

Pediatric
In a population pharmacokinetic analysis of two 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 nonelderly and elderly populations.

Renal Impairment
Mild to moderate renal impairment (CLcr ≥30 mL/min/1.73 m^2) had no influence on plasma concentrations of rosuvastatin.

Hepatic Impairment
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.

Pregnancy Risk Summary

ROSTAT 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 ROSTAT during pregnancy

Lactation Risk Summary

Rosuvastatin use is contraindicated during breastfeeding.

INDICATIONS AND USAGE

ROSTAT is an HMG Co-A reductase inhibitor indicated for:

Hyperlipidemia and Mixed Dyslipidemia

ROSTAT 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.

Pediatric Patients with Familial Hypercholesterolemia

ROSTAT 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

ROSTAT is indicated as adjunctive therapy to diet for the treatment of adult patients with hypertriglyceridemia.

Primary Dysbetalipoproteinemia (Type III Hyperlipoproteinemia)

ROSTAT 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

ROSTAT 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

ROSTAT 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, ROSTAT is indicated to:

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

Limitations of use

ROSTAT has not been studied in Fredrickson Type I and V dyslipidemias.

DOSAGE AND ADMINISTRATION

General Dosing Information

The dose range for ROSTAT in adults is 5 to 40 mg orally once daily. 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 ROSTAT dose of 40 mg should be used only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose.

ROSTAT can be administered as a single dose at any time of day, with or without food.

When initiating ROSTAT therapy or switching from another HMG-CoA reductase inhibitor therapy, the appropriate ROSTAT 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 ROSTAT, lipid levels should be analyzed within 2 to 4 weeks and the dosage adjusted accordingly.

Pediatric Dosing

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.

Dosing in Patients with Severe Renal Impairment

For patients with severe renal impairment (CLcr <30 mL/min/1.73 m^2) not on hemodialysis, dosing of ROSTAT should be started at 5 mg once daily and not exceed 10 mg once daily.

DOSAGE FORMS AND STRENGTHS

5 mg: Yellow, round, biconvex, film coated tablets.
10 mg: Blue, elliptical, biconvex, film coated one side scored tablets.
20 mg: Orange, elliptical, biconvex, film coated one side scored tablets.

CONTRAINDICATIONS

ROSTAT is 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.
- Patients with active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels.
- Pregnancy.
- Lactation. Limited data indicate that rosuvastatin is present in human milk. Because statins have the potential for serious adverse reactions in nursing infants, women who require ROSTAT 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 ROSTAT. These risks can occur at any dose level, but are increased at the highest dose (40 mg).

ROSTAT should be prescribed with caution in patients with predisposing factors for myopathy (e.g., age ≥ 65 years, inadequately treated hypothyroidism, renal impairment).

The risk of myopathy during treatment with ROSTAT may be increased with concurrent administration of some other lipid-lowering therapies (fibrates or niacin), gemfibrozil, cyclosporine, atazanavir/ritonavir, lopinavir/ritonavir, or simeprevir.

ROSTAT therapy should be discontinued if markedly elevated creatine kinase levels occur or myopathy is diagnosed or suspected.

All patients should be advised to promptly report to their physician unexplained muscle pain, tenderness, or weakness.

Liver Enzyme Abnormalities

It is recommended that liver enzyme tests be performed before the initiation of ROSTAT, and if signs or symptoms of liver injury occur.

ROSTAT 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 ROSTAT.

Concomitant Coumarin Anticoagulants

Caution should be exercised when anticoagulants are given in conjunction with ROSTAT.

Proteinuria and Hematuria

A dose reduction should be considered for patients on ROSTAT therapy with unexplained persistent proteinuria and/or hematuria during routine urinalysis testing.

Endocrine Effects

ROSTAT alone does not reduce basal plasma cortisol concentration or impair adrenal reserve; caution should be exercised if ROSTAT is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

ADVERSE REACTIONS

Rostat is generally well tolerated. Adverse reactions have usually been mild and transient.

The most commonly reported adverse reactions (incidence ≥2%) in the rosuvastatin are:

- Headache
- Myalgia
- Abdominal pain
- Asthenia
- Nausea

The most common adverse reactions that led to treatment discontinuation are:

- Myalgia
- Abdominal pain
- Nausea