Rosera™ Tablets

(Rosuvastatin)

DESCRIPTION:
Rosuvastatin calcium is a synthetic lipid-lowering agent for oral administration

Rosuvastatin calcium is a white amorphous powder that is sparingly soluble in water and methanol, and slightly soluble in ethanol. Rosuvastatin calcium is a hydrophilic compound with a partition coefficient (octanol/water) of 0.13 at pH of 7.0

COMPOSITION:

Rosera™ 5mg tablets
Each film coated tablet contains:
Rosuvastatin Calcium Ph. Eur.
eq. to Rosuvastatin ….….. 5mg

Rosera™ 10mg tablets
Each film coated tablet contains:
Rosuvastatin Calcium Ph. Eur.
eq. to Rosuvastatin .....…. 10mg

Rosera™ 20mg tablets
Each film coated tablet contains:
Rosuvastatin Calcium Ph. Eur.
eq. to Rosuvastatin ….….. 20mg

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. 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: Peak plasma concentrations of rosuvastatin reached 3 to 5 hours following oral dosing. Both C_{max} 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, 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. After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route

INDICATIONS AND USAGE:
Hyperlipidemia and Mixed Dyslipidemia: Rosuvastatin 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 nonpharmacological interventions alone have been inadequate
Paediatric Patients 10 to 17 years of age with Heterozygous Familial Hypercholesterolemia (HeFH): Adjunct to diet to reduce Total-C, LDL-C and ApoB levels in adolescent boys and girls, who are at least one year post-menarche, 10-17 years of age with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy, the following findings are present: LDL-C > 190mg/dL or > 160mg/dL and there is a positive family history of premature cardiovascular disease (CVD) or two or more other CVD risk factors
Hypertriglyceridemia: Rosuvastatin is indicated as adjunctive therapy to diet for the treatment of adult patients with hypertriglyceridemia
Primary Dysbetalipoproteinemia (Type III Hyperlipoproteinemia): Rosuvastatin is indicated as an adjunct to diet for the treatment of patients with primary dysbetalipoproteinemia (Type III hyperlipoproteinemia)
Homozygous Familial Hypercholesterolemia: Rosuvastatin 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: Rosuvastatin 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, hs-CRP > 2mg/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, rosuvastatin is indicated to:

- Reduce 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:
The dose range for rosuvastatin is 5 to 40mg orally once daily. The usual starting dose is 10-20mg. Rosuvastatin can be administered as a single dose at any time of day, with or without food. When initiating rosuvastatin therapy or switching from another HMG-CoA reductase inhibitor therapy, the appropriate rosuvastatin 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 rosuvastatin, lipid levels should be analyzed within 2 to 4 weeks and the dosage adjusted accordingly
Heterozygous Familial Hypercholesterolemia in Paediatric Patients (10 to 17 years of age): The usual dose range of rosuvastatin is 5-20mg/day; the maximum recommended dose is 20mg/day (doses greater than 20mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy. Adjustments should be made at intervals of 4 weeks or more
Homozygous Familial Hypercholesterolemia: The recommended starting dose of rosuvastatin is 20mg once daily. Response to therapy should be estimated from preapheresis LDL-C levels
Use with Cyclosporine, Lopinavir/Ritonavir or Atazanavir/Ritonavir: In patients taking cyclosporine, the dose of rosuvastatin should be limited to 5mg once daily. In patients taking a combination of lopinavir and ritonavir or atazanavir and ritonavir, the dose of rosuvastatin should be limited to 10mg once daily
Concomitant Lipid-Lowering Therapy: The risk of skeletal muscle effects may be enhanced when rosuvastatin is used in combination with niacin or fenofibrate; a reduction in rosuvastatin dosage should be considered in this setting . Combination therapy with gemfibrozil should be avoided because of an increase in rosuvastatin exposure with concomitant use; if rosuvastatin is used in combination with gemfibrozil, the dose of rosuvastatin should be limited to 10mg once daily
Dosage in Patients with Severe Renal Impairment: For patients with severe renal impairment (CrCl <30mL/min/1.73 m^2) not on hemodialysis, dosing of rosuvastatin should be started at 5mg once daily and not exceed 10mg once daily

OR
As directed by the physician

CONTRAINDICATIONS:
Rosera™ 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
- Women who are pregnant or may become pregnant: Because HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, rosuvastatin may cause fetal harm when administered to pregnant women. Additionally, there is no apparent benefit to therapy during pregnancy, and safety in pregnant women has not been established. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and the lack of known clinical benefit with continued use during pregnancy
- Nursing mothers: Because another drug in this class passes into breast milk, and because HMG-CoA reductase inhibitors have the potential to cause serious adverse reactions in nursing infants, women who require rosuvastatin treatment should be advised not to nurse 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
Rosuvastatin 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 rosuvastatin may be increased with concurrent administration of some other lipid-lowering therapies (fibrates or niacin), gemfibrozil, cyclosporine, lopinavir/ritonavir, or atazanavir/ritonavir
Rosuvastatin therapy should be discontinued if markedly elevated creatinine 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). All patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever

Liver Enzyme Abnormalities and Monitoring
It is recommended that liver enzyme tests be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g. semiannually) thereafter. Increases in serum transaminases [AST (SGOT) or ALT (SGPT)] have been reported with HMG-CoA reductase inhibitors, including rosuvastatin

Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of rosuvastatin is recommended. Rosuvastatin 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 rosuvastatin
Concomitant Coumarin Anticoagulants: Caution should be exercised when anticoagulants are given in conjunction with rosuvastatin because of its potentiation of the effect of coumarin-type anticoagulants in prolonging the prothrombin time/INR. In patients taking coumarin anticoagulants and rosuvastatin concomitantly, INR should be determined before starting rosuvastatin and frequently enough during early therapy to ensure that no significant alteration of INR occurs
Endocrine Effects: Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including rosuvastatin

ADVERSE REACTIONS:
- Rhabdomyolysis with myoglobinuria and acute renal failure and myopathy (including myositis)
- Liver enzyme abnormalities

The most common adverse reactions that led to treatment discontinuation were: Myalgia, abdominal pain and nausea

The most commonly reported adverse reactions (incidence ≥ 2%) were: Headache, myalgia, abdominal pain, asthenia and nausea

DRUG INTERACTIONS:
Cyclosporine: Significantly increased rosuvastatin exposure. Therefore, in patients taking cyclosporine, therapy should be limited to rosuvastatin 5mg once daily
Gemfibrozil: Significantly increased rosuvastatin exposure. Therefore, combination therapy with rosuvastatin and gemfibrozil should be avoided. If used, do not exceed rosuvastatin 10mg once daily
Protease Inhibitors: Coadministration of rosuvastatin with certain protease inhibitors given in combination with ritonavir has differing effects on rosuvastatin exposure. The protease inhibitor combinations lopinavir/ritonavir and atazanavir/ritonavir increase rosuvastatin exposure (AUC) up to threefold. For these combinations the dose of rosuvastatin should be limited to 10mg. The combinations of tipranavir/ritonavir or fosamprenavir/ritonavir produce little or no change in rosuvastatin exposure. Caution should be exercised when rosuvastatin is coadministered with protease inhibitors given in combination with ritonavir
Coumarin Anticoagulants: Rosuvastatin significantly increased INR in patients receiving coumarin anticoagulants. Therefore, caution should be exercised when coumarin anticoagulants are given in conjunction with rosuvastatin. In patients taking coumarin anticoagulants and rosuvastatin concomitantly, INR should be determined before starting rosuvastatin 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 rosuvastatin is used in combination with niacin; a reduction in rosuvastatin dosage should be considered in this setting
Fenofibrate: When rosuvastatin was coadministered with fenofibrate, no clinically significant increase in the AUC of rosuvastatin or fenofibrate was observed. The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates should be carefully weighed against the potential risks of this combination
Concomitant Use of Antacids: When taking rosuvastatin with an aluminum and magnesium hydroxide combination antacid, the antacid should be taken at least 2 hours after rosuvastatin administration

USE IN SPECIAL POPULATIONS:
Pregnancy
Teratogenic effects: Pregnancy Category X: Rosuvastatin is contraindicated in women who are or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy and cholesterol products are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hyperlipidemia therapy

There have been rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors. Pregnancies in women exposed to other HMG-CoA reductase inhibitors, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed the rate expected in the general population. Rosuvastatin may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking rosuvastatin, the patient should be apprised of the potential risks to the fetus and the lack of known clinical benefit with continued use during pregnancy
Nursing Mothers: It is not known whether rosuvastatin is excreted in human milk, but a small amount of another drug in this class does pass into breast milk. Because another drug in this class passes into human milk and because HMG-CoA reductase inhibitors have a potential to cause serious adverse reactions in nursing infants, women who require rosuvastatin treatment should be advised not to nurse their infants
Paediatric Use: Patients treated with 5mg, 10mg, and 20mg daily rosuvastatin had an adverse experience profile generally similar to that of patients treated with placebo. The same warnings and precautions for adults should be considered for children and adolescents. There was no detectable effect of rosuvastatin on growth, weight, BMI (body mass index), or sexual maturation in paediatric patients (10 to 17 years of age). Adolescent females should be counseled on appropriate contraceptive methods while on rosuvastatin therapy
Geriatric Use: Elderly patients are at higher risk of myopathy and rosuvastatin should be prescribed with caution in the elderly
Renal Impairment: Rosuvastatin exposure is not influenced by mild to moderate renal impairment (CrCl ≥ 30mL/min/1.73m^2); however, exposure to rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment who are not receiving hemodialysis. Rosuvastatin dosing should be adjusted in patients with severe renal impairment (CrCl <30mL/min/1.73 m^2) not requiring hemodialysis
Hepatic Impairment: Rosuvastatin 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; rosuvastatin should be used with caution in these patients

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

Drug-Drug Interactions: Cytochrome P450 3A4: Rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent

Effect of Coadministered Drugs on Rosuvastatin Systemic Exposure:

Coadministered drug and dosing regimen	Rosuvastatin		
	Dose (mg)*	Change in AUC**	Change in C_{max}**
Cyclosporine - stable dose required (75mg - 200mg BID)	10mg QD for 10 days	↑ 7-fold†	↑ 11-fold†
Gemfibrozil 600mg BID for 7 days	80mg	↑ 1.9-fold†	↑ 2.2-fold†
Lopinavir/ritonavir combination 400mg/100mg BID for 10 days	20mg QD for 7 days	↑ 2-fold†	↑ 5-fold†
Atazanavir/ritonavir combination 300mg/100mg QD for 7 days	10mg	↑ 3-fold†	↑ 7-fold†
Tipranavir/ritonavir combination 500mg/200mg BID for 11 days	10mg	↑ 26%	↑ 2-fold
Fosamprenavir/ritonavir 700mg/100mg BID for 7 days	10mg	↑ 8%	↑ 45%
Fenofibrate 67mg TID for 7 days	10mg	↑ 7%	↑ 21%
Aluminum & magnesium hydroxide combination antacid: Administered simultaneously Administered 2 hours apart	 40mg 40mg	 ↓ 54%† ↓ 22%	 ↓ 50%† ↓ 16%
Erythromycin 500mg QD for 7 days	80mg	↓ 20%	↓ 31%
Ketoconazole 200mg BID for 7 days	80mg	↑ 2%	↓ 5%
Itraconazole 200mg QD for 5 days	10mg 80mg	↑ 39% ↑ 28%	↑ 36% ↑ 15%
Fluconazole 200mg QD for 11days	80mg	↑ 14%	↑ 9%

*Single dose unless otherwise noted
**Mean ratio (with/without coadministered drug and no change = 1-fold) or % change (with/without coadministered drug and no change = 0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively
† Clinically significant

Effect of Rosuvastatin Coadministration on Systemic exposure to other Drugs:

Rosuvastatin dosage regimen	Coadministered drug		
	Name and Dose	Change in AUC	Change in C_{max}
40mg QD for 10 days	Warfarin* 25mg single dose	R-Warfarin ↑ 4% S-Warfarin ↑ 6%	R-Warfarin ↓1% S-Warfarin 0%
40mg QD for 12 days	Digoxin 0.5mg single dose	↑ 4%	↑ 4%
40mg QD for 28 days	Oral contraceptive (ethinyl estradiol 0.035mg and norgestrel 0.180, 0.215 and 0.250mg) QD for 21 days	EE ↑ 26% NG ↑ 34%	EE ↑ 25% NG ↑ 23%

EE = ethinyl estradiol, NG = norgestrel
*Clinically significant pharmacodynamic effects

STABILITY:
See expiry on the pack

PRESENTATION:
Rosera™ 5mg tablets in a pack of 10's
Rosera™ 10mg tablets in a pack of 10's
Rosera™ 20mg tablets in a pack of 10's

INSTRUCTIONS:
Keep out of reach of children. Avoid exposure to heat, light and humidity
Store between 15 to 30ºC. Improper storage may deteriorate the medicine

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com

روزیرا™ ٹیبلٹ
(روزیوواسٹیٹن)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں
بچوں کی پہنچ سے دور رکھیں
دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ
کے درمیان رکھیں ورنہ دوا خراب ہو جائیگی