**Rosuvastatin Calcium**

(Crestor®, AstraZeneca)

**Classification:** Antihyperlipidemic, Cardiovascular Agent, HMG-CoA Reductase Inhibitor

**Pharmacology:**
Rosuvastatin selectively and competitively inhibits HMG-CoA reductase, the rate-limiting enzyme in the production of mevalonate, a cholesterol precursor. Rosuvastatin has high activity in, uptake into, and selectivity for the liver, the target organ. It enhances uptake and catabolism of LDL by increasing hepatic LDL receptor levels. It also inhibits the hepatic VLDL synthesis, reducing total number of VLDL and LDL particles.

**Pharmacokinetics:**
- **Absorption:** Peak plasma concentrations reached 3-5 hours after oral dose. $C_{\text{max}}$ and AUC proportionately increases with rosuvastatin dose. Bioavailability 20%. Food has no effect on AUC. AUC does not differ between morning and evening doses.
- **Distribution:** Volume of distribution 134 L, 88% protein bound (mostly albumin)
- **Metabolism:** Not extensively metabolized; major metabolite has one-sixth to one-half inhibitory activity of parent. Greater than 90% of activity attributed to parent compound.
- **Elimination:** Oral: 90% excreted in feces; elimination $t_{1/2}$ 19 hours. IV: 28% renally cleared; 72% hepatically cleared

**Indications:**
Adjunctive therapy to diet used for treatment of adult patients with primary hyperlipidemia or mixed dyslipidemia, treatment of heterozygous familial hypercholesterolemia (HeFH) in ages 10-17, hypertriglyceridemia, primary dysbetalipoproteinemia (Type III hyperlipoproteinemia), and slowing atherosclerosis progression. Adjunctive therapy to other lipid-lowering treatments to treat adults with homozygous familial hypercholesterolemia. Also used to prevent cardiovascular disease by reducing risks of stroke, myocardial infarction, and arterial revascularization procedures.

**Dosage:**
- **General:** rosuvastatin dose range is 5 to 40 mg orally once daily. Starting dose is usually 10 to 20 mg. Can administer single dose any time of the day with or without food. Swallow tablets whole. When initiating rosuvastatin or switching from another HMG-CoA reductase inhibitor, use appropriate starting dose then titrate based on patient’s response and goal of therapy. Lipid levels should be analyzed 2 to 4 weeks after initiation or titration of therapy and adjust dose accordingly. 40 mg dose should only be used in patients who did not achieve LDL-C goal with 20 mg dose.
- **HeFH in pediatrics patients:** usual rosuvastatin dose is 5-20 mg/day; max 20 mg/day; dose adjustments at intervals of 4 weeks or more.
- **Homozygous familial hypercholesterolemia:** recommended rosuvastatin starting dose is 20 mg once daily; assess response to therapy from prepheresis LDL-C levels.
- **Asian patients** have increased plasma rosuvastatin levels; consider 5 mg once daily as initial dose.
Use with concomitant therapy:
Patients concomitantly taking cyclosporine: rosuvastatin max dose of 5 mg once daily.
Patients concomitantly taking gemfibrozil: rosuvastatin initial therapy of 5 mg once daily; should not exceed 10 mg once daily.
Patients concomitantly taking lopinavir and ritonavir or atazanavir and ritonavir: rosuvastatin initial therapy of 5 mg once daily; should not exceed 10 mg once daily.¹

Patients with severe renal impairment (CrCl < 30 mL/min/1.73m²) not on hemodialysis should initiate rosuvastatin therapy at 5 mg once daily; should not exceed 10 mg once daily. Plasma concentration is increased 3-fold in severe renal impairment.¹

Contraindications
- Known hypersensitivity to any component of product. Reported hypersensitivity reactions include rash, pruritis, urticaria, and angioedema
- Active liver disease including unexplained persistent hepatic transaminase level elevations
- Pregnant or may become pregnant
- Nursing mothers¹

Warnings and Precautions:
- Risk of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria; risk increased with highest dose (40 mg)
- Caution when prescribing to patients with predisposing factors for myopathy (eg: renal impairment, age ≥ 65, inadequate hypothyroid treatment)
- Increased risk of myopathy with concurrent use of fibrates, niacin (especially ≥ 1 gram per day), cyclosporine, lopinavir/ritonavir, or atazanavir/ritonavir
- Liver enzyme tests should be performed prior to rosuvastatin initiation due to risk of liver enzyme abnormalities
- Use caution with administering rosuvastatin in conjunction with anticoagulants due to risk of prolonging prothrombin time/INR. It is recommended to monitor INR until stable upon initiation or alteration of rosuvastatin therapy.
- Risk of proteinuria and hematuria
- Risk of increases in HbA1c and fasting glucose levels¹

Adverse Reactions:
- Serious adverse reactions: rhabdomyolysis with myoglobinuria, acute renal failure, myopathy, and liver enzyme abnormalities
- Most common adverse effects leading to treatment discontinuation during clinical trials (1.4% of patients): myalgia, abdominal pain, nausea
- Most common adverse reactions reported (incidence ≥ 2% of patients): headache (3.1% to 8.5%), myalgia (1.9% to 12.7%), abdominal pain (2.4%), asthenia (0.9% to 4.7%), nausea (up to 6.3%)
- Children treated with rosuvastatin had more frequent elevations in serum creatine phosphokinase (>10 x ULN) compared to children treated with placebo (4/130, 3% vs 0/46, 0%).¹²

Interactions:
- Not significantly dependent on cytochrome P450 3A4 metabolism
- Substrate for certain transporter proteins (OATP1B1 and BCRP); therefore, increased rosuvastatin exposure (AUC) with concurrent use of cyclosporine (7-fold increase), gemfibrozil (2-fold increase), and certain protease inhibitors (lopinavir/ritonavir, atazanavir/ritonavir (2 to 3-fold increase))
- Concurrent use of rosuvastatin with coumarin anticoagulants significantly increases INR
- Lipid-modifying doses of niacin (≥1 g/day) in combination with rosuvastatin enhances risk of skeletal muscle effects
- Simultaneous administration of aluminum and magnesium hydroxide significantly decreases rosuvastatin exposure by 54% (administration 2 hours apart decreases AUC only 22%)
- HMG-CoA reductase inhibitors known to increase risk of myopathy when concurrently used with fenofibrate; use caution with concurrent use
- Myopathy reported with coadministration of HMG-CoA reductase inhibitors with colchicine

**Special Populations:**
- **Pregnancy:** teratogenic effects (pregnancy category X)
- **Nursing mothers:** unknown whether rosuvastatin passes in human milk; advised to avoid rosuvastatin in nursing mothers due to another drug in this class known to pass into human breast milk
- **Pediatrics:** same warnings and precautions as adults should be applied to patients ages 10 to 17; no controlled clinical trials performed on children less than 10 years of age
- **Geriatrics:** no differences in effectiveness between geriatric and younger subjects; however, there is a higher risk of myopathy in elderly patients, so use rosuvastatin with caution
- **Renal impairment:** dose adjust in patients with severe renal impairment not receiving dialysis
- **Hepatic impairment:** contraindicated in patients with active liver disease

**Costs and Monitoring:**
- Daily cost is $6.40 for once a day dosing.

Lipid panel should be monitored 2 to 4 weeks after initiation and after dosage adjustments. Liver function must be monitored at baseline and when clinically indicated. High risks for abnormal liver function include large alcohol consumption and a history of chronic liver disease.

**How Supplied:**
- Tablet: 5 mg, 10 mg, 20 mg, 40 mg

**Efficacy:**
- **Hyperlipidemia and Mixed Dyslipidemia:**
  - In a multicenter, double-blind, placebo-controlled, dose-ranging study, significant reduction in total-C, LDL-C, non-HDL-C, ApoB, and TG and increase in HDL-C were seen across all dose ranges of a single rosuvastatin daily dose for 6 weeks. In an active-controlled study, when compared to other HMG-CoA reductase inhibitors (atorvastatin, simvastatin, pravastatin), a more significant reduction in LDL-C was seen with rosuvastatin.

- **Heterozygous familial hypercholesterolemia:**
  - In an active-controlled study, significant reductions from baseline in LDL-C seen in patients treated with 6 weeks of rosvastatin 20 mg (-47% from baseline LDL-C) followed by 6 weeks of rosvastatin 40 mg (-55% from baseline LDL-C).

- **Hypertriglyceridemia:**
  - In a double-blind, placebo-controlled dose-response study, 6 weeks of a single daily dose (5 to 40 mg) rosuvastatin significantly reduced serum TG levels (median of -21% from baseline with 5 mg, -37% from baseline with 10 mg, -37% from baseline with 20 mg, and -43% from baseline with 40 mg) compared to changes in TG with the placebo (median of 1% from baseline).
Primary Dysbetalipoproteinemia:
In a randomized, multicenter, double-blind crossover study, rosuvastatin showed to reduce non-HDL-C and circulating remnant lipoprotein levels when used in conjunction with the Therapeutic Lifestyle Change (TLC) diet.¹

Homozygous familiar hypercholesterolemia:
In a dose-titration study, LDL-C was reduced by 22% from baseline when rosuvastatin dose was titrated from 20 mg to 40 mg after 6 weeks.¹

HeFH in pediatric patients:
In a double blind, randomized, multicenter, placebo-controlled study, the levels of LDL-C, total cholesterol, and ApoB levels were significantly reduced on patients given rosuvastatin. The LDL-C goal of < 100 mg/dL were achieved by 0% for placebo whereas the goals were met in subjects taking rosuvastatin: 5 mg (12% of subjects), 10 mg (41%), and 20 mg (41%).¹

Atherosclerosis progression:
In the Measuring Effects on Intima Media Thickness: an Evaluation Of Rosuvastatin 40 mg (METEOR) study, a double-blind, placebo-controlled clinical study, 984 patients were randomized to a 5:2 ratio of rosuvastatin or placebo. The rate of change of the mean maximum carotid intima-media thickness at 12 sites was determined by ultrasonograms. 52.1% of patients treated with rosuvastatin had an absence of disease progression compared to 37.7% in the placebo group.¹

Cardiovascular disease primary prevention:
In the Justification for the Use of Statins in Primary Prevent: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, 17,802 men and women with no cardiovascular disease were assessed for the occurrence of major cardiovascular disease events. The subjects were randomly assigned to either the placebo (n=8901) or rosuvastatin 20 mg once daily (n=8901) group. The subjects were followed for two years, though the study terminated early due to meeting predefined stopping rules. The primary end point was the first-time occurrence of major CV events (nonfatal myocardial infarction, nonfatal stroke, or hospitalization due to unstable angina or arterial revascularization). Significant risk reductions of major CV events were seen in subjects given rosuvastatin (252 events in placebo group vs 142 events in rosuvastatin group) with statistically significant (p<0.001) relative risk reduction of 44% and absolute risk reduction of 1.2%. No significant differences were seen between the placebo and rosuvastatin groups for death due to CV reasons or unstable angina. Rosuvastatin significantly reduced the risk of myocardial infarction (6 fatal and 62 nonfatal events in placebo group vs 9 fatal and 22 nonfatal events in rosuvastatin group) and risk of stroke (6 fatal and 58 nonfatal events in placebo group vs 3 fatal and 30 nonfatal events in rosuvastatin group).¹

Comparison between rosuvastatin and atorvastatin:
The Crestor® Athero Imaging Head to Head IVUS Study (SATURN), which was a 104-week, randomized, double-blind, parallel group, multi-center Phase IIIb study, compared the efficacy between rosuvastatin 40 mg and atorvastatin 80 mg in treating atherosclerotic disease burden measured by intravascular ultrasound in coronary artery disease patients. After 104 weeks of therapy, patients treated with rosuvastatin had lower levels of LDL cholesterol than those treated with atorvastatin (62.6 vs. 70.2 mg/dL, p<0.001) and higher levels of HDL cholesterol (50.4 vs. 48.6 mg/dL, p=0.01). Although rosuvastatin achieved lower LDL levels and higher HDL levels, both groups had a similar degree of regression of percent atheroma volume, indicating their equal efficacy in achieving the primary endpoint.⁴
In a randomized trial, 120 patients with STEMI were assigned 1:1 to atorvastatin (80 mg/day) or rosuvastatin (20 mg/day). The lipid profile, values of oxidized-LDL, tumor necrosis factor receptor 1 and 2, interleukin-6, and hs-CRP were compared between the two groups after 4 weeks of therapy. Both groups had decreased levels of LDL-C, oxidized-LDL, hs-CRP, tumor necrosis factor receptor 1 and 2, and interleukin-6 according to baseline. The only difference between these two groups was a slight decrease in HDL-C in the atorvastatin group (-1.4 ± 8.9 mg/dL) versus an increase in HDL-C in the rosuvastatin group (2.0 ± 9.4 mg/dL, p=0.04).\(^5\)

In an open-label randomized trial in a high-risk Pakistani cohort, patients with type 2 diabetes, hypertension, myocardial infarction, or stroke were assigned to receive atorvastatin 10 mg HS or rosuvastatin 5 mg HS daily. After 6 weeks of therapy, patients receiving rosuvastatin had a greater absolute and percent reduction in serum LDL-C levels compared to patients receiving atorvastatin (0.96 mg/dL vs 0.54 mg/dL; p=0.011 and 24.34% vs 13.66%; p=0.045). Reduction in all other fractions of the lipid panel were equal between these two groups.\(^6\)

Special circumstances for using rosuvastatin:
Rosuvastatin is only 10% metabolized, and it is primarily metabolized via the CYP2C9 pathway. On the other hand, atorvastatin is significantly metabolized by the liver, and its major metabolic pathway is via the CYP3A4 pathway. Due to these differences in metabolism of the drugs, rosuvastatin has less drug interactions than atorvastatin. Drug interactions that increase statin exposure can lead to a higher risk for rhabdomyolysis which may be life-threatening.\(^2, 3\)

Conclusions:
High intensity statins are the recommended agents for patients ≤75 years of age with clinical ASCVD, primary prevention in individuals ≥ 21 years of age with LDL-C ≥ 190 mg/dL, and primary prevention in individuals ages 40 to 75 with diabetes and estimated 10-year ASCVD risk of ≥7.5%. In addition, high-intensity statin therapy lowers LDL-C generally by at least 50%.\(^7\) For cases in which a high intensity statin is recommended but drug interactions with atorvastatin are of concern, rosuvastatin could serve as an equally efficacious and potentially safer alternative. Some studies have shown that rosuvastatin is more efficacious than is atorvastatin at lowering LDL-C and/or increasing HDL-C. However, there is a lack of head-to-head comparative studies between atorvastatin and rosuvastatin showing significant benefit of rosuvastatin over atorvastatin with regard to clinical outcomes, such as decreased morbidity and mortality. When the costs of the medications are taken into account, atorvastatin may be the preferred agent.

<table>
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<tr>
<th>Drug</th>
<th>Price per tablet</th>
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<tr>
<td>Rosuvastatin 20 mg, 40 mg</td>
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<tr>
<td>Atorvastatin 40 mg, 80 mg</td>
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Recommendation:
Add rosuvastatin to the formulary as a reserve status for those needing high intensity statin therapy with nonresponse or significant drug-drug interactions with atorvastatin. The generic of this medication should be supplied starting July 2016. If the price of the medication decreases markedly, this medication may be reconsidered for uses other than for special circumstances.
References:
5. Aydin MU, Aygul N, Altunkeser BB, et al. Comparative effects of high-dose atorvastatin
   versus moderate-dose rosuvastatin on lipid parameters, oxidized-LDL and inflammatory
6. Arshad AR. Comparison of low-dose rosuvastatin with atorvastatin in lipid-lowering efficacy
   and safety in a high-risk pakistani cohort: an open-label randomized trial. J Lipids.
   of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the
   American College of Cardiology/American Heart Association Task Force on Practice

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