Rosulin®
(Rosuvastatin)

Highnoon

COMPOSITION
Rosulin 5mg Tablet: Each film-coated tablet contains: Rosuvastatin (as calcium) 5mg

Rosulin 10mg Tablet: Each film-coated tablet contains: Rosuvastatin (as calcium) 10mg

Rosulin 20mg Tablet: Each film-coated tablet contains: Rosuvastatin (as calcium) 20mg

DESCRIPTION
Rosulin (Rosuvastatin Calcium) is a synthetic lipid-lowering agent for oral administration.

MECHANISM OF ACTION
Rosuvastatin Calcium 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 to have a high uptake into, and selectivity for, action in the liver, the target organ for cholesterol lowering. Rosuvastatin produces its lipid-modifying effects in two ways. Firstly, it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL and secondly, rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.

PHARMACOKINETICS
Rosuvastatin is incompletely absorbed from the gastrointestinal tract, with an absolute bioavailability of about 20%. Peak plasma concentrations occur about 5 hours after an oral dose. It is taken up extensively by the liver, its primary site of action and undergoes limited metabolism mainly by cytochrome P450 isoenzyme CYP2C9. It is about 90% bound to plasma proteins. The plasma elimination half-life of Rosuvastatin is about 19 hours. About 90% of an oral dose of Rosuvastatin appears in the faeces, including absorbed and non-absorbed drug and the remainder excreted in the urine; about 5% of a dose is excreted unchanged in the urine.

INDICATIONS AND USAGE
- 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 has been inadequate.
- 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).
- As adjunctive therapy to diet for the treatment of adult patients with hypertriglyceridemia.
- As an adjunct to diet for the treatment of adult patients with primary dysbetalipoproteinemia (Type III Hyperlipoproteinemia).
- 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.
- 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.
- 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, it is indicated to:
  - reduce the risk of stroke
  - reduce the risk of myocardial infarction
  - reduce the risk of arterial revascularization procedures
- It has not been studied in Fredrickson Type I and V dyslipidemias.

DOSAGE AND ADMINISTRATION
General Dosing Information
- The dose range in adults is 5mg to 40mg orally once daily. The usual starting dose is 10mg to 20mg once daily. The usual starting dose in adult patients with homozygous familial hypercholesterolemia is 20mg once daily. The maximum recommended dose of 40mg should be used only for those patients who have not achieved their LDL-C goal utilizing the 20mg dose. It can be administered as a single dose at any time of day, with or without food. The tablet should be swallowed whole. When initiating this therapy or switching from another HMG-CoA reductase inhibitor therapy, the appropriate its 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 its titration, 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 5mg to 10mg orally once daily in patients 8 to less than 10 years of age, and 5mg to 20mg orally once daily in patients 10 to 17 years of age.
- In homozygous familial hypercholesterolemia, the recommended dose is 20mg orally once daily in patients 7 to 17 years of age.

Use with Concomitant Therapy
- Patient taking cyclosporin and darolutamide the dose of (Rosuvastatin) should not exceed 5mg once daily.
- Avoid concomitant use of Rosuvastatin with gemfibrozil. If concomitant use cannot be avoided, initiate Rosuvastatin at 5mg once daily. The dose of Rosuvastatin should not exceed 10mg once daily.
- Patients taking atazanavir and ritonavir, lopinavir and ritonavir, or simeprevir, or combination of dasabuvir/ombitasvir/paritaprevir/ritonavir, elbasvir/grazoprevir, sofosbuvir/velpatasvir and glecaprevir/pibrentasvir initiate Rosuvastatin therapy with 5mg once daily. The dose of Rosuvastatin should not exceed 10mg once daily.
- Patients taking regorafenib, the dose of Rosuvastatin should not exceed 10mg once daily.

Severe Renal Impairment
- For patients with severe renal impairment (CL<30 mL/min/1.73 m²) not on hemodialysis, dosing of Rosuvastatin should be started at 5mg once daily and not exceed 10mg once daily.

CONTRAINDICATIONS
Rosuvastatin calcium tablets are 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.

WARNING 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 (40mg). 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 (other fibrates or niacin), gemfibrozil, cyclosporine, darolutamide, regorafenib, atazanavir/ritonavir, lopinavir/ritonavir, simeprevir or combination of sofosbuvir / velpatasvir / voxilaprevir, dasabuvir/ombitasvir/paritaprevir/ritonavir, elbasvir/grazoprevir, sofosbuvir/velpatasvir, glecaprevir/pibrentasvir, all combinations with ledipasvir (including ledipasvir/sofosbuvir). Cases of myopathy, including rhabdomyolysis, have been reported with HMG-CoA reductase inhibitors, including rosuvastatin, co-administered with colchicine, and caution should be exercised when prescribing Rosuvastatin with colchicine. 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). 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. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. There have been rare reports of fatal and non-fatal hepatic failure in patients taking statins, including rosuvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with Rosuvastatin, promptly interrupt therapy. If an alternate etiology is not found, do not restart Rosuvastatin. 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.

Proteinuria and Hematuria
Dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin treated patients. Though it was generally transient and was not associated with worsening renal function. Although the clinical significance of this finding is unknown, a dose reduction should be considered for patients on rosuvastatin 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. Although, Rosuvastatin alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if rosuvastatin is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

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 before starting Rosuvastatin and frequently enough during early therapy to ensure that no significant alteration of INR occurs.

Immune-Mediated Necrotizing Myopathy
There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required. Consider risk of IMNM carefully prior to initiation of a different statin. If therapy is initiated with a different statin, monitor for signs and symptoms of IMNM.

ADVERSE REACTIONS
The reported adverse events of Rosuvastatin are rhabdomyolysis with myoglobinuria, acute renal failure and myopathy, liver enzyme abnormalities, myalgia, asthenia, abdominal pain, nausea, pharyngitis, headache, diarrhea, dyspepsia, nausea, back pain, flu syndrome, urinary tract infection, rhinitis, sinusitis, accidental injury, chest pain, infection, pain, pelvic pain, neck pain, hypertension, angina pectoris, vasodilatation, palpitation, constipation, gastroenteritis, vomiting, flatulence, periodontal abscess, gastritis, diabetes mellitus, anemia, ecchymosis, peripheral edema, arthritis, arthralgia, pathological fracture, dizziness, sleep disorder (insomnia and nightmares), hypertonia, paresthesia, peripheral neuropathy, depression, anxiety, vertigo, neuralgia, bronchitis, cough increased, dyspnea, pneumonia, asthma, rash, pruritus, arrhythmia, hepatitis, hypersensitivity reactions (i.e., face edema, thrombocytopenia, leukopenia, vesiculobullous rash, urticaria, angioedema), kidney failure, syncope, myasthenia, myositis, pancreatitis, photosensitivity reaction, myopathy, rhabdomyolysis, dipstick-positive proteinuria, microscopic hematuria, elevated creatinine phosphokinase, transaminases, hyperglycemia, glutamyl transpeptidase, jaundice, alkaline phosphatase, bilirubin, interstitial lung disease, gynecomastia, thyroid function abnormalities, rare reports of immune-mediated necrotizing myopathy and rare reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion).

DRUG INTERACTIONS
- 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.
- Cyclosporine increased rosuvastatin exposure (AUC) 7-fold. Therefore, in patients taking cyclosporine, the dose of Rosuvastatin should not exceed 5 mg once daily.
- Gemfibrozil significantly increased rosuvastatin exposure. Due to an observed increased risk of myopathy/rhabdomyolysis, combination therapy with Rosuvastatin and gemfibrozil should be avoided. If used together, the dose of Rosuvastatin should not exceed 10mg once daily.
- Coadministration 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 Rosuvastatin should not exceed 10mg 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.
- 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 Rosuvastatin.
- 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 Rosuvastatin.
- Cases of myopathy, including rhabdomyolysis, have been reported with HMG-CoA reductase inhibitors, including rosuvastatin, co-administered with colchicine, and caution should be exercised when prescribing Rosuvastatin with colchicine.

USE IN SPECIFIC POPULATIONS
Pregnancy
Rosuvastatin 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. 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. Rosuvastatin should be discontinued as soon as pregnancy is recognized.

Lactation
Rosuvastatin use is contraindicated during breastfeeding. Because of the potential for serious adverse reactions in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with Rosuvastatin.

Females and males of reproductive potential
Contraception
Rosuvastatin may cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with Rosuvastatin.

Pediatric Use
In children and adolescents 8 to 17 years of age with heterozygous familial hypercholesterolemia, the safety and effectiveness of Rosuvastatin as an adjunct to diet to reduce total cholesterol, LDL-C, and ApoB levels when, after an adequate trial of diet therapy, LDL-C exceeds 190 mg/dL or when LDL-C exceeds 160 mg/dL and there is a positive family history of premature CVD or two or more other CVD risk factors, were established. The long-term efficacy of Rosuvastatin therapy initiated in childhood to reduce morbidity and mortality in adulthood has not been established.
Children and adolescents 7 to 15 years of age with homozygous familial hypercholesterolemia were studied, the safety profile was in consistent with that of the previously established safety profile in adults.

Geriatric Use
No overall differences in safety or effectiveness between the elderly and younger patients were observed, but greater sensitivity of some older individuals cannot be ruled out. 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 (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.

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.

DOSAGE INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of the reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

PRESENTATION
Rosulin 5mg Tablets:
Alu. Alu. Blister Pack of 1x10's.

Rosulin 10mg Tablets:
Alu. Alu. Blister Pack of 1x10's.

Rosulin 20mg Tablets:
Alu. Alu. Blister Pack of 1x10's.

روزولن®
(روسواسٹیٹن)

خوراک و ہدایات:
صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

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