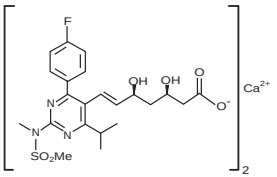
Rovista™
(ROSUVASTATIN)

روّسٹا

Tablets 5mg, 10mg, 20mg

DESCRIPTION
ROVISTA (Rosuvastatin), a synthetic lipid-lowering agent for oral administration. 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. The molecular formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2Ca$. Its structural formula is:



Rosuvastatin calcium

QUANTITATIVE & QUALITATIVE COMPOSITION
ROVISTA (Rosuvastatin) is available for oral administration as:

1. ROVISTA Tablets 5mg
   Each film-coated tablet contains:
   Rosuvastatin…5mg
   (as calcium salt)

2. ROVISTA Tablets 10mg
   Each film-coated tablet contains:
   Rosuvastatin…10mg
   (as calcium salt)

3. ROVISTA Tablets 20mg
   Each film-coated tablet contains:
   Rosuvastatin…20mg
   (as calcium salt)

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-methyl glutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering. Rosuvastatin increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

Pharmacokinetics
Absorption
Maximum plasma concentration is achieved approximately in 5 hours after oral administration. The absolute bioavailability is approximately 20%. Both peak concentration (Cmax) and area under the plasma concentration-time curve (AUC) increased in approximate proportion to rosuvastatin dose.
Administration of rosuvastatin with food did not affect the AUC of rosuvastatin.

Distribution
Rosuvastatin is taken up extensively by the liver which is the primary site of cholesterol synthesis and LDL-C clearance. The volume of distribution of rosuvastatin is approximately 134 L. Approximately 90% of rosuvastatin is bound to plasma proteins, mainly to albumin. This binding is reversible and independent of plasma concentrations.

Metabolism
Rosuvastatin undergoes limited metabolism (approximately 10%). The main metabolites identified are the N-desmethyl and lactone metabolites. The N-desmethyl metabolite is approximately 50% less active than rosuvastatin whereas the lactone form is considered clinically inactive. Rosuvastatin accounts for greater than 90% of the circulating HMG-CoA reductase inhibitor activity.

Excretion
About 90% of an oral dose of rosuvastatin appears in the feces, including absorbed and non-absorbed drugs, and the remainder is excreted in the urine; about 5% of a dose is excreted unchanged in urine. The plasma elimination half-life is approximately 19 hours. The elimination half-life does not increase at higher doses

Special Populations
Race
There is an approximate 2-fold elevation in median AUC and Cmax in Asian Patients compared with Caucasians.

Renal Insufficiency
Patients with varying degrees of renal insufficiency, mild to moderate renal disease had no influence on plasma concentration of rosuvastatin or the N-desmethyl metabolite. Patients with severe insufficiency (creatinine clearance <30 mL/min) had a 3-fold increase in plasma concentration and a 9-fold increase in the N-desmethyl metabolite concentration compared to healthy volunteers. Steady-state plasma concentrations of rosuvastatin in patients undergoing haemodialysis were approximately 50% greater compared to healthy volunteers.

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

THERAPEUTIC INDICATIONS
ROVISTA (Rosuvastatin) is indicated for the treatment of:
1. *Hyperlipidemia and Mixed Dyslipidemia*
   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.

2. *Pediatric Patients 10 to 17 years of age with Heterozygous Familal 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 postmenarche, 10-17 years of age with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present: LDL-C greater than 190 mg/dL or greater than 160 mg/dL and there is a positive family history of premature cardiovascular disease (CVD) or two or more other CVD risk factors.

3. *Hypertriglyceridemia*
   As adjunctive therapy to diet for the treatment of adult patients with hypertriglyceridemia.

4. *Primary Dysbetalipoproteinemia (Type III Hyperlipoproteinemia)*
   As an adjunct to diet for the treatment of patients with primary dysbetalipoproteinemia (Type III Hyperlipoproteinemia).

5. *Homozygous Familal Hypercholesterolemia*
   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.

6. *Slowing of the Progression of Atherosclerosis*
   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.

7. *Prevention of Cardiovascular Events*
   Prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors.

DOSAGE AND ADMINISTRATION
General
The dose range for Rovista (Rosuvastatin) is 5mg to 40mg orally once daily. The usual starting dose is 10-20mg.

Rovista (Rosuvastatin) can be administered as a single dose at any time of day, with or without food.
When initiating Rovista (Rosuvastatin) therapy or switching from another HMG-CoA reductase inhibitor therapy, the appropriate Rovista (Rosuvastatin) starting dose should first be utiized, and only then titrated according to the patient's response and individualized goal of therapy. After initiation or upon titration of Rovista (Rosuvastatin), lipid levels should be analyzed within 2 to 4 weeks and the dosage adjusted accordingly.
The 40mg dose of Rovista (Rosuvastatin) should be used only for those patients who have not achieved their LDL-C goal utiizing the 20mg.

Heterozygous Familal Hypercholesterolemia in Pediatric Patients (10 to 17 years of age)
The usual dose range of Rovista (Rosuvastatin) is 5mg/day to 20mg/day; the maximum recommended dose is 20mg/day. Doses should be individualized according to the recommended goal of therapy. Adjustments should be made at intervals of 4 weeks or more.

Homozygous Familal Hypercholesterolemia
The recommended starting dose of Rovista (Rosuvastatin) is 20mg once daily. Response to therapy should be estimated from pre-apheresis LDL-C levels.

Elderly
A start dose of 5mg is recommended in patients >70 years. No other dose adjustment is necessary in relation to age.

Dosage in patients with renal insufficiency
The recommended start dose is 5mg in patients with moderate renal insufficiency (creatinine clearance of <60mL/min).

Race
The recommended start dose is 5 mg for patients of Asian ancestry. The dose may be increased at intervals of 4 weeks, if necessary, to a usual maximum of 20mg once daily.

Dosage in patients with pre-disposing factors to myopathy
The recommended start dose is 5mg in patients with predisposing factors to myopathy. The dose may be increased at intervals of 4 weeks, if necessary, to a usual maximum of 20mg once daily.

CONTRAINDICATIONS
Rosuvastatin is contraindicated:
- In patients with hypersensitivity to rosuvastatin or to any of the excipients.
- In patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminases elevation exceeding 3x the upper limit of normal (ULN).
- During pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.
- In patients with severe renal insufficiency (Creatinine clearance <30mL/min.)
- In patients with myopathy.
- In patients receiving concomitant cyclosporine.
- In children younger than 10 years.
- Concomitant use of protease inhibitors in HIV patients.

The 40mg dose is contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:
- Moderate renal insufficiency (Creatinine clearance <60mL/min)
- Hypothyroidism.
- Personal or family history of hereditary muscular disorders.
- Previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate.
- Alcohol abuse.
- Situations where an increase in plasma levels may occur.
- Concomitant use of fibrates.
- Asian patients.

ADVERSE REACTIONS
Rosuvastatin is generally well tolerated. Adverse reactions have usually been mild and transient.

Common:
Headache, dizziness, constipation, nausea, abdominal pain, myalgia, asthenia, diabetic mellitus.

Uncommon:
Pruritus, rash and urticaria.

Rare:
Hypersensitivity reactions including angioedema, myopathy, rhabdomyolysis, pancreatitis.

PRECAUTIONS
- Rosuvastatin should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include: renal insufficiency, hypothyroidism, personal or family history of hereditary muscular disorders, previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate, alcohol abuse, age >70 years, situations where an increase in plasma levels may occur, concomitant use of fibrates. In such patients the risk of treatment should be considered in relation to possible benefit and clinical monitoring is recommended. If creatinine kinase levels are significantly elevated at baseline (>5xULN) treatment should not be started.
- There is an increase in serum transaminases [AST (SGOT) or ALT (SGPT)] with HMG-CoA reductase inhibitors, including rosuvastatin. 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. If 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.
- A dose reduction should be considered for patients on rosuvastatin therapy with unexplained persistent proteinuria and/or hematuria during routine urinalysis testing.
- There is an increase in HbA1c and fasting serum glucose levels with HMG-CoA reductase inhibitors, including rosuvastatin. 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.

Drug Interactions
Coumarin
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.

Gemfibrozil
Gemfibrozil significantly increased rosuvastatin exposure. Therefore, combination therapy with rosuvastatin and gemfibrozil should be avoided. If used, do not exceed rosuvastatin 10mg once daily.

Antacid
The simultaneous dosing of rosuvastatin with an antacid suspension containing aluminium and magnesium hydroxide resulted in a decrease in rosuvastatin plasma concentration of approximately 50%. The antacid should be taken atleast 2 hours after rosuvastatin administration.

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.

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. Liver function and creatinine kinase levels should be monitored. Haemodialysis is unlikely to be of benefit.

STORAGE
Store at 25°C (Excursions permitted between 15°C to 30°C). Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
ROVISTA (Rosuvastatin) Tablets 5mg are available in blister pack of 10's.
ROVISTA (Rosuvastatin) Tablets 10mg are available in blister pack of 10's.
ROVISTA (Rosuvastatin) Tablets 20mg are available in blister pack of 10's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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