Rosuvastatin

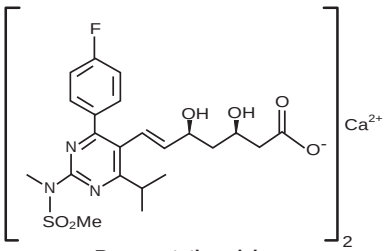
Rovista®

5mg, 10mg, 20mg Tablet

Anti-hypercholesterolaemia/ Anti-dyslipidaemia

DESCRIPTION

Rosuvastatin (Rovista®), a synthetic lipid-lowering agent, is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. 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 empirical formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2Ca$. Its structural formula is:



Rosuvastatin calcium

FORMULATION

Rosuvastatin (Rovista®) is available for oral administration as:

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

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

3. Rosuvastatin (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-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering. 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

Maximum plasma concentration is achieved approximately in 5 hours after oral administration. The absolute bioavailability is approximately 20%. Both peak concentration (C_{max}) and area under the plasma concentration-time curve (AUC) increased in approximate proportion to rosuvastatin dose.

Administration of rosuvastatin with food decreased the rate of drug absorption by 20% as assessed by C_{max}, but there was no effect on the extent of absorption as assessed by AUC.

Distribution

Rosuvastatin is taken up extensively by the liver which is the primary site of cholesterol synthesis and LDL-C clearance. Mean volume of distribution at steady state of rosuvastatin is approximately 134 litres. 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%). The major metabolite is N-desmethyl (50% less active than parent), which is formed principally by cytochrome P450 2C9, and lactone metabolites (clinically inactive). Rosuvastatin accounts for greater than 90% of the circulating HMG-CoA reductase inhibitor activity.

Excretion

Following oral administration, rosuvastatin and its metabolites are primarily excreted in the feces (90%) and approximately 5% is excreted unchanged in the urine. The elimination half-life ($t_{1/2}$) of rosuvastatin is approximately 19 hours. The elimination half-life does not increase at higher doses.

Special Populations

Renal Insufficiency

Subjects with varying degrees of renal impairment, mild to moderate renal disease had little influence on plasma concentrations of rosuvastatin. However, subjects with severe impairment (Cr_{Cl}<30mL/min) had a 3-fold increase in plasma concentration compared to healthy volunteers. Steady-state plasma concentration of rosuvastatin in patients on chronic haemodialysis were approximately 50% greater compared with healthy volunteer subjects with normal renal function.

Hepatic Insufficiency

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.

Drug-Drug Relationship

Cyclosporine:

Co-administration of cyclosporine with rosuvastatin resulted in 11 and 7-fold increase in C_{max} and AUC of rosuvastatin respectively, compared with healthy subjects.

Gemfibrozil:

Co-administration of a single rosuvastatin dose to healthy volunteers on gemfibrozil (600mg twice daily) resulted in a 2.2 and 1.9-fold increase in mean C_{max} and mean AUC of rosuvastatin, respectively.

Antacid:

Co-administration of an antacid (aluminium and magnesium hydroxide combination) with rosuvastatin (40mg) resulted in a decrease in plasma concentrations of rosuvastatin by approximately 50%.

Oral contraceptives:

Co-administration of oral contraceptives (ethinyl estradiol and norgestrel) with rosuvastatin resulted in an increase in plasma concentrations of ethinyl estradiol and norgestrel by 26% and 34%, respectively.

Erythromycin:

Concomitant use of rosuvastatin and erythromycin resulted in a 20% decrease in AUC and a 30% decrease in C_{max} of rosuvastatin.

THERAPEUTIC INDICATIONS

Rosuvastatin (Rovista®) is indicated:

- To reduce elevated total-C, LDL-C, non HDL-C, ApoB, and triglycerides levels and to increase HDL-C in patients with homozygous familial hypercholesterolaemia and mixed dyslipidaemia as adjunct to diet and other non-pharmacological or lipid lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable or inadequate.
- As an adjunct to diet for the treatment of patients with elevated serum TG levels (Hypertriglyceridaemia/Fredrickson Type IV).

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving Rosuvastatin (Rovista®) and should continue on this diet during treatment with Rosuvastatin (Rovista®). Rosuvastatin (Rovista®) can be administered as a single dose at any time of day, with or without food.

Homozygous Familial Hypercholesterolaemia

The recommended starting dose of Rosuvastatin (Rovista®) is 20mg once daily in patients with homozygous familial hypercholesterolaemia. The maximum recommended daily dose is 40mg. Rosuvastatin (Rovista®) should be used in these patients as an adjunct to other lipid-lowering treatments.

The following guidelines may be used to establish treatment goals:

NCEP Treatment Guidelines
LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD* or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129:drug optional)**
2+ Risk factors (10-year risk ≤ 20%)	<130	≥130	≥130 10-year risk 10-20%
			≥160 10-year risk <10%
0-1 Risk factor #	<160	≥160	≥190 (160-189) (LDL-lowering drug optional)

* CHD-coronary heart disease.

** Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

\# Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

Mixed Dyslipidaemia (Fredrickson Types IIa and IIb)
The dose range for Rosuvastatin (Rovista®) is 5mg to 40mg once daily. Therapy with Rosuvastatin (Rovista®) should be individualized according to goal of therapy and response. The usual recommended starting dose of Rosuvastatin (Rovista®) is 10mg once daily. Initiation of therapy with 5mg once daily may be considered for patients requiring less aggressive LDL-C reductions or who have predisposing factors for myopathy. For patients with marked hypercholesterolaemia (LDL-C>190mg/dL) and aggressive lipid targets, a 20mg starting dose may be considered. After initiation and/or upon titration of Rosuvastatin (Rovista®), lipid levels should be analysed within 2 to 4 weeks and dosage adjusted accordingly. The 40mg dose of Rosuvastatin (Rovista®) is reserved only for those patients who have not achieved their LDL-C goal utilizing the 20mg dose of Rosuvastatin (Rovista®) once daily.

Elevated serum TG levels (Hypertriglyceridaemia/Fredrickson Type IV).
The dose range for Rosuvastatin (Rovista®) is 5mg to 40mg once daily. Usual starting dosage is 10mg per day with adjustments based on lipid levels, monitored once daily 2 to 4 weeks until desired level is achieved.

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

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

Uncommon:
Pruritus, rash and urticaria.

Rare:
Hypersensitivity reactions including angioedema, myopathy, rhabdomyolysis, arthralgia, increased hepatic transaminases.

Very Rare:
Jaundice, hepatitis, polyneuropathy.

Laboratory Abnormalities:
Proteinuria has been observed in patients treated with rosuvastatin. This finding was more frequent in patients taking rosuvastatin 40mg, when compared to lower doses of rosuvastatin.
Other abnormal laboratory values reported were elevated creatinine phosphokinase, dose related increase in transaminases, hyperglycemia, glutamyl transpeptidase, alkaline phosphatase, bilirubin and thyroid function abnormalities.

CONTRAINDICATIONS
Rosuvastatin is contraindicated:
- In patients allergic to any component of the product.
- 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 impairment (Creatinine clearance <30mL /min.)
- In patients with myopathy.
- In patients receiving concomitant cyclosporine.

The 40mg dose is contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:
- Moderate renal impairment (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.

PRECAUTIONS
- Before instituting therapy with rosuvastatin, an attempt should be made to control hypercholesterolaemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems.
- When initiating statin therapy or switching from another statin therapy, the appropriate rosuvastatin starting dose should first be utilized and only then titrated according to the patient's individualized goal of therapy.
- HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. It is recommended that liver function tests be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose and periodically thereafter.

Paediatric Use
Safety and efficacy have not been established in children.

Drug Interactions
Warfarin
Co-administration of rosuvastatin to patients on stable warfarin therapy resulted in clinically significant rises in INR (>4, baseline 2-3).

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.

Antacid:
The antacid should be taken at least 2 hours after rosuvastatin administration.

STORAGE CONDITIONS
Store at temperatures not exceeding 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

AVAILABILTY
Rosuvastatin (Rovista®) 5mg is available in alu-alu blister pack of 10 tablets.

Rosuvastatin (Rovista®) 10mg is available in alu-alu blister pack of 10 tablets.

Rosuvastatin (Rovista®) 20mg is available in alu-alu blister pack of 10 tablets.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Keep out of reach of children.

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

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