

Rosuvax

(Rosuvastatin)

روزيوويكس

COMPOSITION

Each **Rosuvax** 5mg tablet contains 5 mg of rosuvastatin (as calcium).
Each **Rosuvax** 10mg tablet contains 10 mg of rosuvastatin (as calcium).
Each **Rosuvax** 20mg tablet contains 20 mg of rosuvastatin (as calcium).

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 vitro studies in human cells have shown rosuvastatin to have a high uptake into, and selectivity for, action in 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: In clinical pharmacology studies in man, peak plasma concentrations of rosuvastatin were reached 3 to 5 hours following oral dosing. Both Cmax and AUC increased in approximate proportion to rosuvastatin dose. The absolute bioavailability of rosuvastatin is approximately 20%. Administration of rosuvastatin with food did not affect the AUC of rosuvastatin. The AUC of rosuvastatin does not differ following evening or morning drug administration.

Distribution: 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 (t1/2) of rosuvastatin is approximately 19 hours.

Race: Pharmacokinetic studies, including one conducted in the US, have demonstrated an approximate 2-fold elevation in median exposure (AUC and Cmax) in Asian subjects when compared with a Caucasian control group.

Gender: There were no differences in plasma concentrations of rosuvastatin between men and women.

Geriatric: There were no differences in plasma concentrations of rosuvastatin between the nonelderly and elderly populations (age ≥ 65 years).

Renal Impairment: Mild to moderate renal impairment (CLcr ≥ 30 mL/min/1.73 m²) had no influence on plasma concentrations of rosuvastatin. However, plasma concentrations of rosuvastatin increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment (CLcr < 30 mL/min/1.73 m²) not receiving hemodialysis compared with healthy subjects (CLcr > 80 mL/min/1.73 m²).

Hemodialysis: Steady-state plasma concentrations of rosuvastatin in patients on chronic hemodialysis were approximately 50% greater compared with healthy volunteer subjects with normal renal function.

Hepatic Impairment: 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.

INDICATIONS

Hyperlipidemia and Mixed Dyslipidemia: **Rosuvax** is indicated as adjunctive therapy to diet to reduce elevated total-C, LDL-C, ApoB, non HDL-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 non-pharmacological interventions alone has been inadequate.

Hypertriglyceridemia: **Rosuvax** is indicated as adjunctive therapy to diet for the treatment of adult patients with hypertriglyceridemia. Primary Dysbetalipoproteinemia (Type III Hyperlipoproteinemia): **Rosuvax** is indicated as an adjunct to diet for the treatment of patients with primary dysbetalipoproteinemia (Type III Hyperlipoproteinemia).

Homozygous Familial Hypercholesterolemia: **Rosuvax** 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: **Rosuvax** 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

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

General Dosing Information: The dose range for **Rosuvax** is 5 to 40 mg orally once daily. **Rosuvax** can be administered as a single dose at any time of day, with or without food. When initiating **Rosuvax** therapy or switching from another HMG-CoA reductase inhibitor therapy, the appropriate **Rosuvax** starting dose should first be utilized, and only then titrated according to the patient's response and individualized goal of therapy. The 40 mg dose of **Rosuvax** should be used only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose.

Hyperlipidemia, Mixed Dyslipidemia, Hypertriglyceridemia, Primary Dysbetalipoproteinemia (Type III Hyperlipoproteinemia) and Slowing of the Progression of Atherosclerosis: The recommended startig dose of **Rosuvax** is 10 mg once daily. For patients with marked hyperlipidemia (LDL-C > 190 mg/dL) and aggressive lipid targets, a 20 mg starting dose may be considered. After initiation or upon titration of **Rosuvax**, lipid levels should be analyzed within 2 to 4 weeks and the dosage adjusted accordingly. Homozygous Familial Hypercholesterolemia: The recommended starting dose of **Rosuvax** is 20 mg once daily. Response to therapy should be estimated from pre-apheresis LDL-C levels.

Dosage in Asian Patients: Initiation of **Rosuvax** therapy with 5 mg once daily should be considered for Asian patients. Use with Cyclosporine or Lopinavir/Ritonavir: In patients taking cyclosporine, the dose of **Rosuvax** should be limited to 5 mg once daily. In patients taking a combination of lopinavir and ritonavir, the dose of **Rosuvax** should be limited to 10 mg once daily. Concomitant Lipid-Lowering Therapy: The risk of skeletal muscle effects may be enhanced when **Rosuvax** is used in combination with niacin or fenofibrate; a reduction in **Rosuvax** dosage should be considered in this setting. Combination therapy with gemfibrozil should be avoided because of an increase in **Rosuvax** exposure with concomitant use; if **Rosuvax** is used in combination with gemfibrozil, the dose of **ROSUVAX** should be limited to 10 mg once daily.

Dosage in Patients With Severe Renal Impairment: For patients with severe renal impairment (CLcr < 30 mL/min/1.73 m²) not on hemodialysis, dosing of rosuvastatin should be started at 5 mg once daily and not exceed 10 mg once daily.

UNDESIRABLE EFFECTS

The adverse events seen with rosuvastatin are generally mild and transient. In controlled clinical trials, less than 4% of rosuvastatin treated patients were withdrawn due to adverse events.

The frequencies of adverse events are ranked according to the following: Common (>1/100, <1/10); Uncommon (>1/1,000, <1/100); Rare (>1/10,000, <1/1000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

Immune system disorders

Rare: hypersensitivity reactions including angioedema

Nervous system disorders

Common: headache, dizziness

Gastrointestinal disorders

Common: constipation, nausea, abdominal pain

Rare: pancreatitis

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash and urticaria

Musculoskeletal, connective tissue and bone disorders

Common: myalgia

Rare: myopathy (including myositis) and rhabdomyolysis

General disorders

Common: asthenia

As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to be dose dependent. Renal Effects: Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with rosuvastatin. Shifts in urine protein from none or trace to ++ or more were seen in <1% of patients at some time during treatment with 10 and 20 mg, and in approximately 3% of patients treated with 40 mg. A minor increase in shift from none or trace to + was observed with the 20 mg dose. In most cases, proteinuria decreases or disappears spontaneously on continued therapy. Review of data from clinical trials and post-marketing experience to date has not identified a causal association between proteinuria and acute or progressive renal disease. Haematuria has been observed in patients treated with rosuvastatin and clinical trial data show that the occurrence is low. Skeletal muscle effects: Effects on skeletal muscle e.g. myalgia, myopathy (including myositis) and, rarely, rhabdomyolysis with and without acute renal failure have been reported in rosuvastatin treated patients with all doses but are increased at the highest dose(40mg). A dose-related increase in CK levels has been observed in patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient. If CK levels are elevated (>5xULN), treatment should be discontinued.

Liver Effects: As with other HMG-CoA reductase inhibitors, a dose-related increase in transaminases has been observed in a small number of patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of rosuvastatin:: arthralgia, hepatitis, jaundice and memory loss. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

DRUG INTERACTIONS

Cyclosporine: Cyclosporine significantly increased rosuvastatin exposure. Therefore, in patients taking cyclosporine, therapy should be limited to rosuvastatin 5 mg once daily.

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

Lopinavir/Ritonavir: The combination of lopinavir and ritonavir significantly increased rosuvastatin exposure. Therefore, in patients taking a combination of lopinavir and ritonavir, the dose of rosuvastatin should be limited to 10 mg once daily. The effect of other protease inhibitors on rosuvastatin pharmacokinetics has not been examined.

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.

Ezetimibe: Concomitant use of rosuvastatin and ezetimibe resulted in no change to AUC or Cmax for either drug. However, a pharmacodynamic interaction, in terms of adverse effects, between rosuvastatin and ezetimibe cannot be ruled out.

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%. This effect was mitigated when the antacid was dosed 2 hours after rosuvastatin. The clinical relevance of this interaction has not been studied.

Erythromycin: Concomitant use of rosuvastatin and erythromycin resulted in a 20% decrease in AUC (0-t) and a 30% decrease in Cmax of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Oral contraceptive/hormone replacement therapy (HRT): Concomitant use of rosuvastatin and an oral contraceptive resulted in an increase in ethinyl estradiol and norgestrel AUC of 26% and 34%, respectively. These increased plasma levels should be considered when selecting oral contraceptive doses. There are no pharmacokinetic data available in subjects taking concomitant rosuvastatin and HRT and therefore a similar effect cannot be excluded. However, the combination has been extensively used in women in clinical trials and was well tolerated.

Other medicinal products: Based on data from specific interaction studies no clinically relevant interaction with digoxin is expected.

Cytochrome P450 enzymes: Results from in vitro and in vivo studies show that rosuvastatin is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes. In addition, rosuvastatin is a poor substrate for these isoenzymes. Therefore, drug interactions resulting from cytochrome P450-mediated metabolism are not expected.

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 (40 mg). 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, or lopinavir/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. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. In a pooled analysis of placebo-controlled trials, increases in serum transaminases to >3 times the upper limit of normal occurred in 1.1% of patients taking rosuvastatin versus 0.5% of patients treated with placebo. 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 anti-coagulants 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.

Proteinuria and Hematuria: In the rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin treated patients. These findings were more frequent in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator HMG-CoA reductase inhibitors, 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: Although clinical studies have shown that 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.

Use In Specific Populations

Pregnancy: 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.

Nursing Mothers: It is not known whether rosuvastatin is excreted in human 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.

Pediatric Use: The safety and effectiveness of rosuvastatin in pediatric patients have not been established. Treatment experience with rosuvastatin in a pediatric population is limited to 8 patients with homozygous FH. None of these patients was below 8 years of age. In a pharmacokinetic study, 18 patients (9 boys and 9 girls) 10 to 17 years of age with heterozygous FH received single and multiple oral doses of rosuvastatin. Both Cmax and AUC of rosuvastatin were similar to values observed in adult subjects administered the same doses.

Geriatric Use: No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, 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); 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 (CLcr < 30 mL/min/1.73 m²) 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.

Asian Patients: Pharmacokinetic studies have demonstrated an approximate 2-fold increase in median exposure to rosuvastatin in Asian subjects when compared with Caucasian controls. Rosuvastatin dosage should be adjusted in Asian patients.

OVERDOSE

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.

CONTRAINDICATIONS

Rosuvastatin is contraindicated in the following conditions:

- Patients with a known hypersensitivity to any component of this product.
- Patients with active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels.
- Women who are pregnant or may become pregnant.
- Nursing mothers.

PRESENTATION

Rosuvax tablet 5mg: 1x10's/pack.
Rosuvax tablet 10mg: 1x10's/pack.
Rosuvax tablet 20mg: 1x10's/pack.

Dosage:

As directed by the physician.

Instructions:

Store below 30°C.
Protect from sunlight & moisture.
Keep out of reach of children.

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Detailed prescribing information is available on request.



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An ISO Certified Company

LFT/038/01

خوراک:
ڈاکٹر کی ہدایت کے مطابق۔

ہدایات:
دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔