Xovat®
(Rosuvastatin)
5 mg, 10 mg, 20 mg Tablets

زواٹ
(رُسوواسٹیٹین)
۵ ملی گرام، ۱۰ ملی گرام، ۲۰ ملی گرام ٹیبلیٹس

QUALITATIVE & QUANTITATIVE COMPOSITION

Xovat 5mg Tablets
Each film-coated tablet contains:
Rosuvastatin as Rosuvastatin Calcium (USP).....5mg
Xovat 10mg Tablets
Each film-coated tablet contains:
Rosuvastatin as Rosuvastatin Calcium (USP).....10mg
Xovat 20mg Tablets
Each film-coated tablet contains:
Rosuvastatin as Rosuvastatin Calcium (USP).....20mg

DESCRIPTION

Xovat (Rosuvastatin) is a synthetic lipid-lowering agent for oral administration.
The chemical name for 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 $(C_{22}H_{27}FN_3O_6S)_2Ca$ and the molecular weight is 1001.14.

CLINICAL INFORMATION

Indications

Hyperlipidemia and Mixed Dyslipidemia
Xovat (Rosuvastatin) is indicated 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 is inadequate.

Pediatric Patients with Familial Hypercholesterolemia
Xovat (Rosuvastatin) is indicated as an adjunct to diet to:
• Reduce Total-C, LDL-C and ApoB levels in children and adolescents 8 to17 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).

Hypertriglyceridemia
Xovat (Rosuvastatin) is indicated as adjunctive therapy to diet for the treatment of adult patients with hypertriglyceridemia.

Primary Dysbetalipoproteinemia (Type III Hyperlipoproteinemia)
Xovat (Rosuvastatin) is indicated as an adjunct to diet for the treatment of adult patients with primary dysbetalipoproteinemia (Type III Hyperlipoproteinemia).

Adult Patients with Homozygous Familial Hypercholesterolemia
Xovat (Rosuvastatin) 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
Xovat (Rosuvastatin) 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
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, Xovat (Rosuvastatin) is indicated to:
• reduce the risk of stroke
• reduce the risk of myocardial infarction
• reduce the risk of arterial revascularization procedures

Limitations of Use
Data regarding the use of Xovat (Rosuvastatin) in Fredrickson Type I and V dyslipidemias in not available.

Dosage and administration

Adult dosage
The dose range for Xovat (Rosuvastatin) in adults is 5 to 40 mg orally once daily. The usual starting dose is 10 to 20 mg once daily. The usual starting dose in adult patients with homozygous familial hypercholesterolemia is 20 mg once daily.
The maximum Xovat (Rosuvastatin) dose of 40 mg should be used only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose.
When initiating Xovat (Rosuvastatin) therapy or switching from another HMG-CoA reductase inhibitor therapy, the appropriate Xovat (Rosuvastatin) 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 titration of Xovat (Rosuvastatin), lipid levels should be analysed within 2 to 4 weeks and the dosage adjusted accordingly.

Pediatric Dosage
In heterozygous familial hypercholesterolemia, the recommended dose range is 5 to 10 mg orally once daily in patients 8 to less than 10 years of age, and 5 to 20 mg orally once daily in patients 10 to 17 years of age. In homozygous familial hypercholesterolemia, the recommended dose is 20 mg orally once daily in patients 7 to 17 years of age.

Dosage adjustment
Dosing in Asian Patients
In Asian patients, consider initiation of Xovat (Rosuvastatin) therapy with 5 mg once daily due to increased rosuvastatin plasma concentrations. The increased systemic exposure should be taken into consideration when treating Asian patients not adequately controlled at doses up to 20 mg/day.
Renal Impairment
For patients with severe renal impairment (CLcr <30 mL/min/1.73 m^2) not on hemodialysis, dosing of Xovat (Rosuvastatin) should be started at 5 mg once daily and not exceed 10 mg once daily.
Geriatric Use
Elderly patients are at higher risk of myopathy, caution should be exercised.
Renal Impairment
Exposure to Rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment (CLcr <30 mL/min/1.73 m^2) 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.

Administration requirements
Xovat (Rosuvastatin) can be administered as a single dose at any time of day, with or without food. The tablet should be swallowed whole.

Contraindications
Rosuvastatin is contraindicated in patients with
• A known hypersensitivity to any component of this product.
• Active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels
• Pregnancy
• Lactation

Warnings and Precautions

Skeletal Muscle Effects
Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria may occur with HMG-CoA reductase inhibitors, including Rosuvastatin. These risks 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). This risk may be increased with concurrent administration of some other lipid-lowering therapies. 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). Rarely, immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, may occur with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents. 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
Liver enzyme tests should be performed before the initiation of Rosuvastatin , and if symptoms of liver injury occur. Increases in serum transaminases [AST (SGOT) or ALT (SGPT)] may occur with HMG-CoA reductase inhibitors, including Rosuvastatin. In most cases, the elevations may be transient and resolve or improve on continued therapy or after a brief interruption in therapy. Increases in serum transaminases to >3 times the upper limit of normal may occur in some patients taking Rosuvastatin. Rarely, fatal and non-fatal hepatic failure may occur 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.

Concomitant Coumarin Anticoagulants

Caution should be exercised when anticoagulants are given in conjunction with Rosuvastatin.

Proteinuria and Hematuria

Dipstick-positive proteinuria and microscopic hematuria may be observed with Rosuvastatin which may be more frequent in patients taking Rosuvastatin 40 mg, as compared to lower doses of Rosuvastatin or HMG-CoA reductase inhibitors, though it may be generally transient and is 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 may occur with HMG-CoA reductase inhibitors, including Rosuvastatin. Sometimes, these increases may exceed the threshold for the diagnosis of diabetes mellitus. 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.

Interactions

Cyclosporine

Cyclosporine may increase Rosuvastatin exposure and may result in increased risk of myopathy.

In patients taking cyclosporine, the dose of Rosuvastatin should not exceed 5 mg once daily.

Gemfibrozil

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 10 mg once daily.

Protease Inhibitors

Coadministration of Rosuvastatin with certain protease inhibitors has differing effects on rosuvastatin exposure and may increase risk of myopathy. 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. For these protease inhibitors, the dose of Rosuvastatin should not exceed 10 mg once daily. The combinations of HIV-1 protease inhibitors, produce little or no change in Rosuvastatin exposure. Caution should be exercised.

Coumarin Anticoagulants

Rosuvastatin may significantly increase INR in patients receiving coumarin anticoagulants. Caution should be exercised when coumarin anticoagulants are given in conjunction with Rosuvastatin. In such patients, 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 lipid-modifying doses (≥1 g/day) of niacin; caution should be exercised.

Fenofibrate

Because 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 exercised.

Colchicine

Cases of myopathy, including rhabdomyolysis, may occur with HMG-CoA reductase inhibitors, including rosuvastatin, coadministered with colchicine, hence caution should be exercised.

Pregnancy and Breastfeeding

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. Rosuvastatin may cause fetal harm when administered to pregnant women. Rosuvastatin should be discontinued as soon as pregnancy is recognized.

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.

Effects on ability to drive and use machines

Based on its pharmacodynamic properties, Rosuvastatin is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

Adverse Reactions

Blood and lymphatic system disorders	*Rare:* Thrombocytopenia
Immune system disorders	*Rare:* Hypersensitivity reactions including angioedema
Endocrine disorders	*Common:* Diabetes mellitus
Psychiatric disorders	*Not known:* Depression
Nervous system disorders	*Common:* Headache, dizziness *Not known:* Peripheral neuropathy, sleep disturbances (including insomnia and nightmares)
Respiratory, thoracic and mediastinal disorders	*Not known:* Cough, dyspnoea
Gastro-intestinal disorders	*Common:* Constipation, nausea, abdominal pain *Rare:* Pancreatitis *Not known:* Diarrhoea
Hepatobiliary disorders	*Rare:* Increased hepatic transaminases *Very rare:* Jaundice, hepatitis
Skin and subcutaneous tissue disorders	*Uncommon:* Pruritus, rash, urticaria *Not known:* Stevens-Johnson syndrome
Musculo-skeletal and connective tissue disorders	*Common:* Myalgia *Rare:* Myopathy (including myositis), rhabdomyolysis, Lupus-like syndrome, muscle rupture *Not known:* Tendon disorders, sometimes complicated by rupture, immune-mediated necrotising myopathy
Renal and urinary disorders	*Very rare:* Haematuria
Reproductive system and breast disorders	*Very rare:* Gynaecomastia
General disorders and administration site conditions	*Common:* Asthenia *Not known:* Oedema

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.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group

Pharmacotherapeutic group: HMG-CoA reductase inhibitors. ATC code: C10A A07

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. 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.

Pharmacokinetic properties

Absorption

Maximum rosuvastatin plasma concentrations are achieved approximately 5 hours after oral administration. The absolute bioavailability is approximately 20%.

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.

Metabolism

Rosuvastatin undergoes limited metabolism (approximately 10%). CYP2C9 was the principal isoenzyme involved, with 2C19, 3A4 and 2D6 involved to a lesser extent. The main metabolites identified are the N-desmethyl and lactone metabolites. The N-desmethyl metabolite is approximately 50% less active than rosuvastatin. Rosuvastatin accounts for > 90% of the circulating HMG-CoA reductase inhibitor activity.

Elimination

Approximately 90% of the Rosuvastatin dose is excreted unchanged in the faeces (consisting of absorbed and non-absorbed active substance) and the remaining part is excreted in urine. Approximately 5% is excreted unchanged in urine. The plasma elimination half-life is approximately 19 hours. The elimination half-life does not increase at higher doses. As with other HMG-CoA reductase inhibitors, the hepatic uptake of Rosuvastatin involves the membrane transporter OATP-C. This transporter is important in the hepatic elimination of rosuvastatin.

PHARMACEUTICAL INFORMATION

Shelf life

2 years.

Special precautions for storage

Store at (15°C to 30°C). Protect from light, moisture & heat.

Keep medicine out of the reach of children.

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Nature and contents of container

Xovat (Rosuvastatin) 5mg tablets are available in a blister pack of 10's (1 x 10's).
Xovat (Rosuvastatin) 10mg tablets are available in a blister pack of 10's (1 x 10's).
Xovat (Rosuvastatin) 20mg tablets are available in a blister pack of 10's (1 x 10's).

ہدایات:

(15°C سے 30°C) درجہ حرارت پر رکھیں۔
روشنی، نمی اور گرمی سے بچائیں۔ دوا کو بچوں کی پہنچ سے دور رکھیں۔

REVISION DATE
February 2020

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AGP Limited
B-23-C, S.I.T.E., Karachi.

ASPIN
An OBS Group Company

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