X-PLENDED® (Rosuvastatin) ایکس-پلینڈڈ

COMPOSITION

X-Plended 5 mg
Each film coated tablet contains:
Rosuvastatin…… 5 mg
as Rosuvastatin calcium
X-Plended 10 mg
Each film coated tablet contains:
Rosuvastatin…… 10 mg
as Rosuvastatin calcium
X-plended 20 mg
Each film coated tablet contains:
Rosuvastatin…… 20 mg
as Rosuvastatin calcium
(PharmEvo Specs.)

DESCRIPTION

X-Plended is a synthetic anti-hyperlipidemic (lipid-lowering) agent. The empirical formula for Rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2Ca$. Its molecular weight is 1001.14.

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. 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
Peak plasma concentrations of Rosuvastatin are attained 3-5 hours following oral dosing. The absolute bioavailability of Rosuvastatin is approximately 20%.
Distribution
Mean volume of distribution at steady-state of Rosuvastatin is approximately 134 liters. 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 209, and in vitro studies have demonstrated that N-desmethyl Rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of Rosuvastatin. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by Rosuvastatin.
Excretion
Rosuvastatin and its metabolites are primarily excreted in the feces (90%). The elimination half-life (t1/2) of Rosuvastatin is approximately 19 hours.

INDICATIONS

Hyperlipidemia and Mixed Dyslipidemia
X-PLENDED 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.
Pediatric Patients 8 to 17 years of age with Heterozygous Familial Hypercholesterolemia (HeFH)
Adjunct to diet to reduce Total-C, LDL-C and ApoB levels in children and adolescents 8-17 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 and there is a positive family history of premature cardiovascular disease (CVD) or two or more other CVD risk factors
Pediatric Patients 7 to 17 years of age with Homozygous Familial Hypercholesterolemia
Reduce LDL-C, Total-C, non HDL-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
X-PLENDED (Rosuvastatin) is indicated as adjunctive therapy to diet for the treatment of adult patients with hypertriglyceridemia.
Primary Dysbetalipoproteinemia (Type III Hyperlipoproteinemia)
X-PLENDED is indicated as an adjunct to diet for the treatment of patients with primary dysbetalipoproteinemia (Type III Hyperlipoproteinemia).
Homozygous Familial Hypercholesterolemia
X-PLENDED 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
X-PLENDED 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 risk factors for cardiovascular disease, X-PLENDED is indicated to:
• reduce the risk of stroke • reduce the risk of myocardial infarction • reduce the risk of arterial revascularization procedures

DOSAGE AND ADMINISTRATION

General Dosing Information

The dose range for X-PLENDED is 5 to 40 mg orally once daily. The usual starting dose is 10-20 mg. When initiating Rosuvastatin therapy or switching from another HMG-CoA reductase inhibitor therapy, the appropriate 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 Rosuvastatin, lipid levels should be analyzed within 2 to 4 weeks and the dosage adjusted accordingly.

The 40 mg dose of X-PLENDED should be used only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose.

The 40 mg dose is not recommended in patients with pre-disposing risk factors for myopathy or rhabdomyolysis including 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 (exposure to rosuvastatin) may occur, Asian patients, concomitant use of fibrates.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (8 to 17 years of age)
In patients 8 to less than 10 years of age with heterozygous familial hypercholesterolemia, the usual dose range is 5 to 10 mg orally once daily. In patients 10 to 17 years of age with heterozygous familial hypercholesterolemia, the usual dose range is 5 to 20 mg orally once daily. Adjustments should be made at intervals of 4 weeks or more.

Homozygous Familial Hypercholesterolemia in Pediatric Patients (7 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.

Homozygous Familial Hypercholesterolemia
The recommended starting dose of X-PLENDED is 20 mg once daily. Response to therapy should be estimated from preapheresis LDL-C levels.

Dose adjustment in special populations

Dosing in Asian patients
In Asian patients, consider initiation of Rosuvastatin therapy with 5 mg once daily due to increased rosuvastatin plasma concentrations

Dosage in patients receiving other drugs
The dose of rosuvastatin should not exceed 5 mg once daily, in patients taking cyclosporine. In patients taking gemfibrozil, atazanavir and ritonavir, lopinavir and ritonavir or simeprevir, the recommended starting dose is 5 mg once daily and total daily dose should not exceed 10 mg. See DRUG INTERACTIONS

Dosing in patients with Severe Renal Impairment
For patients with severe renal impairment (creatinine clearance <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.

Administration requirements

X-PLENDED can be administered as a single dose at any time of day, with or without food. The tablet should be swallowed whole.

CONTRAINDICATIONS

• Known hypersensitivity to Rosuvastatin
• Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels
• Women who are pregnant or may become pregnant
• Known cases of myopathy
• 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

WARNINGS & PRECAUTIONS

Hepatic effects
Transient or persistent elevations in hepatic transaminases [AST (SGOT) or ALT (SGPT)] can occur. Perform liver enzyme tests before initiating therapy and as clinically indicated thereafter e.g. if signs and symptoms of liver injury occur. Rosuvastatin should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal. In most cases, the elevations are transient and resolve upon continued therapy or after a brief interruption in therapy.

There have been rare post-marketing 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, Rosuvastatin must be discontinued. If an alternate etiology is not found, therapy must not be re-initiated.

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.

Myopathy/Rhabdomyolysis
Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including Rosuvastatin. The risk is highest with the maximum dose (40 mg). Rosuvastatin should be prescribed with caution in patients with predisposing factors for myopathy (e.g. age ≥ 65 years, hypothyroidism, renal impairment, history of hereditary muscular disorders, history of myopathy with statin/fibrate use). In such situations, monitoring of serum creatine kinase (CK) levels is suggested before treatment and if baseline CK levels are significantly elevated (>5xULN), treatment should not be started. The risk of myopathy may also be increased with concurrent administration of some other lipid-lowering drugs (fibrates, niacin, gemfibrozil, ezetimibe or nicotinic acid), cyclosporine, protease inhibitors or colchicine. Use of fibrate with rosuvastatin 40 mg dose is not recommended and use of fusidic acid must be avoided with any dose of Rosuvastatin.
Rosuvastatin therapy should also not be used 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).

There also have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use 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.

Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Rosuvastatin therapy should be discontinued if markedly elevated CK levels occur (>5xULN) or myopathy is diagnosed or suspected. If symptoms resolve and CK levels return to normal, then retreatment with the lowest possible dose and close monitoring may be considered.

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 enough during early therapy to ensure that no significant alteration of INR occurs.

Hyperglycemia
Statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Increases in HbA1c and fasting serum glucose levels have been reported. In some instances these increases may also exceed the threshold for the diagnosis of diabetes mellitus.

Endocrine effects on cortisol
Rosuvastatin alone does not reduce basal plasma cortisol concentration or impair adrenal reserve; however caution should be exercised, if it is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

Renal Effects – Proteinuria and Hematuria
Proteinuria mostly tubular in origin, detected by dipstick testing and microscopic hematuria, has been observed in patients treated with higher doses of Rosuvastatin, in particular 40 mg. These effects are generally transient not associated with worsening renal function. An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg. A dose reduction should be considered for patients on Rosuvastatin therapy with unexplained persistent proteinuria and/or hematuria during routine urinalysis testing.

Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. Presenting features can include dyspnea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected that a patient has developed interstitial lung disease, Rosuvastatin therapy should be discontinued.

Effects on ability to drive or use machines
Rosuvastatin does not impair the ability to drive or use machines. However, it should be considered that dizziness may occur as a side effect with Rosuvastatin.
ADVERSE REACTIONS

Rosuvastatin is generally well tolerated. Adverse reactions seen with Rosuvastatin are generally mild and transient. Adverse reactions from clinical studies and extensive post-marketing experience are listed below according to frequency and system organ class (SOC). Frequencies are ranked as per the following convention: Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Rare: Thrombocytopenia
Immune system disorders
Rare: Hypersensitivity reactions, angioedema
Endocrine disorders
Common: Diabetes mellitus
Eye disorders
Rare: Blurred vision
Psychiatric disorders
Not known: Depression
Nervous system disorders
Common: Headache, Dizziness
Very rare: Polyneuropathy, memory loss
Not known: Peripheral neuropathy, sleep disturbances (insomnia, nightmares)
Respiratory, thoracic and mediastinal disorders
Not known: Cough, dyspnea
Gastrointestinal disorders
Common: Constipation, nausea, abdominal pain
Rare: Pancreatitis
Not known: Diarrhea
Hepatobiliary disorders
Rare: Increased hepatic transaminases
Very rare: Jaundice, hepatitis
Skin and subcutaneous tissue disorders
Uncommon: Pruritis, rash, urticarial
Not known: Stevenson Johnson syndrome
Musculoskeletal and connective tissue disorders
Common: Myalgia
Rare: Myopathy (including myositis), rhabdomyolysis
Very rare: Arthralgia
Not known: Tendon disorders (including rupture)
Renal and urinary disorders
Very Rare: Hematuria
Reproductive system and breast disorders
Very Rare: Gynaecomastia
General disorders and administration site conditions
Common: Asthenia
Not known: Edema

DRUG INTERACTIONS

Transporter protein inhibitors:
Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of Rosuvastatin with drugs that are inhibitors of these transporter proteins such as Cyclosporine and antiviral protease inhibitor drugs may result in increased Rosuvastatin plasma concentrations and an increased risk of myopathy.

Cyclosporine:
Cyclosporine increases rosuvastatin exposure (AUC) 7-fold. Therefore, in patients taking cyclosporine, the dose of Rosuvastatin should not exceed 5 mg daily.

Protease inhibitors:
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 10 mg 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 coadministered with protease inhibitors.

Gemfibrozil and other lipid-lowering drugs:
Gemfibrozil significantly increases 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 10 mg once daily.

Other lipid lowering drugs such as fibrates (e.g. fenofibrate), lipid lowering doses (> or equal to 1g/day) of niacin (nicotinic acid) may also increase the risk of myopathy when given concomitantly with statins, probably because they can produce myopathy when given alone. A pharmacodynamic interaction is expected and patients receiving these drugs should be started on a 5 mg dose.

The 40 mg dose of Rosuvastatin must not be used concomitantly with a fibrate.

Moreover, concomitant use of Rosuvastatin and ezetimibe results in a 1.2 fold increase in AUC of rosuvastatin. Cases of rhabdomyolysis (though very rare) have been reported with the use of Ezetimibe in combination with statins and a pharmacodynamics interaction is also possible. Caution should be exercised with their combined use.

Antacids
The simultaneous dosing of Rosuvastatin with an antacid containing aluminium and magnesium hydroxide may result in a decrease in Rosuvastatin plasma concentration of approximately 50%. This effect can be reduced if the antacid is dosed 2 hours after Rosuvastatin. The clinical relevance of this interaction has not been studied.

Erythromycin
Concomitant use of Rosuvastatin and erythromycin may result in a 20% decrease in AUC and a 30% decrease in Cmax of Rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Coumarin Anticoagulants
Rosuvastatin can significantly increase INR in patients receiving coumarin anticoagulants such as warfarin. Therefore, caution should be exercised when coumarin anticoagulants are given 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.

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

Colchicine
Cases of myopathy, including rhabdomyolysis, have been reported with HMG-CoA reductase inhibitors, including Rosuvastatin, coadministered with colchicine, and caution should be exercised when prescribing Rosuvastatin with colchicine

Fusidic Acid
Interaction studies with rosuvastatin and fusidic acid are not available. As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with rosuvastatin and fusidic acid given concurrently. Therefore, the combination rosuvastatin and fusidic acid is not recommended. If possible, temporary suspension of rosuvastatin treatment is recommended. If unavoidable, patients should be closely monitored.

USE IN SPECIAL POPULATIONS

Pregnancy
US FDA 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 is expected to have little impact on long-term outcomes of primary hyperlipidemia therapy. Hence, the potential risk from inhibition of HMGCoA reductase outweighs the advantage of treatment during pregnancy.

Nursing Mothers
It is not known whether Rosuvastatin is excreted in human milk but a small amount of another drug in this class does pass into breast milk. In rats, breast milk concentrations of rosuvastatin are 3 times higher than plasma levels; however, animal breast milk drug levels may not accurately reflect human breast milk levels. Because another drug in this class passes into human milk and because statins have a potential to cause serious adverse reactions in nursing infants, women who require Rosuvastatin treatment must be advised not to nurse their infants.

Geriatric Use
Elderly patients are at higher risk of myopathy and Rosuvastatin should be prescribed with caution in the elderly.

Pediatric Use
The safety and effectiveness of Rosuvastatin in pediatric patients younger than 8 years of age have not been established. However, Rosuvastatin can be used in patients 8 to 17 years of age with Heterozygous Familial Hypercholesterolemia (HeFH). See INDICATIONS and DOSAGE AND ADMINISTRATION
Pediatric population may be more prone to develop myopathy, therefore recommended pediatric dose recommendations must be followed and upward titration of dose should be made with caution.

Renal Impairment
Rosuvastatin dosing should be adjusted in patients with severe renal impairment (CL cr < 30 mL/min/1.73 m2) not requiring hemodialysis. Patients with mild to moderate impairment (CL cr greater than 30 mL/min/1.73 m2) do not require dosage adjustment. See DOSAGE AND ADMINISTRATION

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. Liver function and CK levels should be monitored. Hemodialysis does not significantly enhance clearance of Rosuvastatin.

PRESENTATION
X-Plended 5 mg: Pack of 10 tablets
X-Plended 10 mg: Pack of 10 tablets
X-plended 20 mg: Pack of 10 tablets

INSTRUCTIONS
Dosage as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.

خوراک وہدایات:
ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
تمام دوائیں بچوں کی پہنچ سے دُور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخہ پر ہی فروخت کی جائے۔
روشنی، گرمی اور نمی سے محفوظ، 30°C سے کم درجہ حرارت پر رکھیں۔

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