For the Use Only of a Registered Medical Practitioner

PRESCRIBING INFORMATION

XOLSTAT TABLETS
(Rosuvastatin Calcium Tablets 5 mg / 10 mg / 20 mg)

COMPOSITION

XOLSTAT 5 mg
Each film coated tablet contains
Rosuvastatin Calcium equivalent to
Rosuvastatin …… 5 mg

XOLSTAT 10 mg
Each film coated tablet contains
Rosuvastatin Calcium equivalent to
Rosuvastatin …… 10 mg

XOLSTAT 20 mg
Each film coated tablet contains
Rosuvastatin Calcium equivalent to
Rosuvastatin …… 20 mg

Excipients:
XOLSTAT 5 mg tablets also contain: Lactose monohydrate, crospovidone, microcrystalline cellulose, sodium citrate, magnesium stearate, opadry yellow (hypromellose, titanium dioxide, polyethylene glycol / macrogol, yellow iron oxide).

XOLSTAT 10 mg & 20 mg tablets also contain: Lactose monohydrate, crospovidone, microcrystalline cellulose, sodium citrate, magnesium stearate, opadry pink (hypromellose, titanium dioxide, polyethylene glycol / macrogol, red iron oxide).

PRODUCT DESCRIPTION

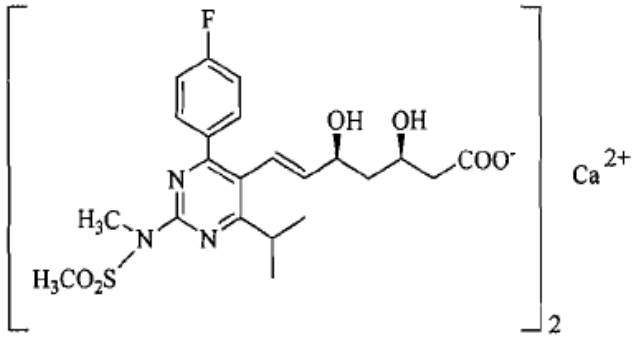
XOLSTAT 5 mg: Light yellow to yellow colored round film coated tablets with 'RT1' on one side and plain on the other side.

XOLSTAT 10 mg: Light pink to pink colored round film coated tablets with 'RT2' on one side and plain on the other side.

XOLSTAT 20 mg: Light pink to pink colored round film coated tablets with 'RT3' on one side and plain on the other side.

DESCRIPTION

XOLSTAT tablets contain rosuvastatin calcium, which is a synthetic lipid-lowering agent for oral administration. The empirical formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2Ca$ and the molecular weight is 1001.14. The chemical name for rosuvastatin calcium is bis[(*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid] calcium salt with the following structural formula:



ROSUVASTATIN CALCIUM

INDICATIONS

Rosuvastatin is indicated as an adjunct to diet, at least equivalent to the Adult Treatment Panel III (ATP III TLC diet), for the reduction of elevated total cholesterol, LDL-cholesterol, ApoB, the total cholesterol: HDL-cholesterol ratio and triglycerides and for increasing HDL-C, in hyperlipedemic and dyslipidemic conditions, when response to diet and exercise alone has been inadequate including:

Prevention of Cardiovascular Events. In adult patients with an increased risk of atherosclerotic cardiovascular disease based on the presence of cardiovascular disease risk markers such as an elevated hsCRP level, age, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, rosuvastatin is indicated to reduce total mortality and the risk of major cardiovascular events (cardiovascular death, stroke, MI, unstable angina, or arterial revascularization).

Rosuvastatin is indicated as an adjunct to diet for the treatment of patients with primary dysbetalipoproteinemia (Type III hyperlipoproteinemia).

Primary hypercholesterolemia (Type IIa excluding heterozygous familial hypercholesterolemia); and severe non-familial hypercholesterolemia).

Combined (mixed) dyslipidemia (Type IIb).

Homozygous familial hypercholesterolemia where rosuvastatin is used either alone or as an adjunct to diet and other lipid lowering treatment such as apheresis.

Rosuvastatin is indicated as adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment surgery to lower Total-C and LDL-C to target levels.

DOSE AND METHOD OF ADMINISTRATION

Patients should be placed on a standard cholesterol-lowering diet (at least equivalent to the Adult Treatment Panel III (ATP III TLC diet)) before receiving rosuvastatin, and should continue on this diet during treatment with rosuvastatin. If appropriate, a program of weight control and physical exercise should be implemented.

Prior to initiating therapy with rosuvastatin, secondary causes for elevations in plasma lipid levels should be excluded. A lipid profile should also be performed. After initiation or upon titration of rosuvastatin, lipid levels should be analyzed within 2-4 weeks and the dosage adjusted accordingly.

The usual recommended starting dose of rosuvastatin is 10 mg once daily. However, initiation of therapy with 5 mg once daily should be considered for special patient populations or patients requiring less aggressive LDL-C reductions. The choice of starting dose should take into account the individual patients' cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions. Rosuvastatin may be taken in the morning or evening with or without food. The majority of patients are controlled at the 10 mg dose. However, if necessary, dose adjustments to the next dose level can be made after 4-week intervals. The maximum response is usually achieved within 2-4 weeks and is maintained during chronic therapy. Increasing the dose to 40 mg should be reserved for patients with severe hypercholesterolemia excluding heterozygous familial hypercholesterolemia at high cardiovascular risk (in particular dose with familial hypercholesterolemia), who do not achieve their treatment goal on 20 mg and should only be initiated under specialist supervision. The physician who elects to use rosuvastatin at a dose higher than 20 mg should periodically re-evaluate the long term risk/benefit of rosuvastatin for the individual patient. Rosuvastatin should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomylosis.

The dosage of rosuvastatin should be individualized according to baseline LDL-C, total-C/HDL-C ratio and/or TG levels, the recommended target lipid values and the patient response.

Lipid levels should be monitored periodically and, if necessary, the dose of rosuvastatin adjusted based on target lipid levels recommended by guidelines.

Dosage in patients with renal insufficiency

The usual dose range applies in patients with mild to moderate renal impairment.
The use of rosuvastatin in patients with severe renal impairment is contraindicated.

Dosage in patients with hepatic insufficiency

There was no increase in systemic exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, increased systemic exposure has been observed in subjects with Child-pugh scores of 8 and 9. In these patients an assessment of renal function should be considered. There is no experience in subjects with Child-Pugh scores above 9. Rosuvastatin is contraindicated in patients with active liver disease.

Use in the elderly

The overall frequency of adverse events and types of adverse events were similar in patients above and below 65 years of age. The efficacy of rosuvastatin in the geriatric population (≥ 65 years of age) was comparable to the efficacy observed in the non-elderly.

Use in Children below 10 years

The safety and effectiveness in children have not been established. In children and adolescents with homozygous familial hypercholesterolemia experience is limited to eight patients (aged 8 years and above).

Dosage on Asian Patients

Initiation of rosuvastatin therapy with 5 mg once daily should be considered for Asian patients. The potential for increased systemic exposures relative to Caucasians is relevant when considering escalation of dose in cases where hypercholesterolemia excluding heterozygous familial hypercholesterolemia is not adequately controlled at doses of 5, 10 or 20 mg once daily.

Concomitant therapy

The effect of rosuvastatin on LDL-C and total-C may be enhanced when used in combination with a bile acid binding resin. If rosuvastatin is used in combination with gemfibrozil, the dose of rosuvastatin should be limited to 10 mg once daily.

Interactions requiring dose adjustments

Gemfibrozil: Increased systemic exposure to rosuvastatin has been observed in subjects taking concomitant rosuvastatin and gemfibrozil. Patients taking this combination should not exceed a dose of rosuvastatin 10 mg once daily (see WARNINGS AND PRECAUTIONS AND DRUG INTERACTIONS).

Dosage in patients with pre-disposing factors to myopathy

The recommended start dose is 5 mg in patients with predisposing factors to myopathy.

Concomitant therapy

Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when rosuvastatin is administered concomitantly with certain medicinal

products that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g. certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir, and/or tipranavir). Whenever possible, alternative medications should be considered, and, if necessary, consider temporarily discontinuing rosuvastatin therapy. In situations where co-administration of these medicinal products with rosuvastatin is unavoidable, the benefit and the risk of concurrent treatment and rosuvastatin dosing adjustments should be carefully considered.

CONTRAINDICATIONS

XOLSTAT (rosuvastatin) tablets are contraindicated in:

- patients with hypersensitivity to rosuvastatin or to any of the excipients of the product. Hypersensitivity reactions including rash, pruritus, urticaria, and angioedema have been reported with rosuvastatin (see UNDESIRABLE EFFECTS).
- patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 times the upper limit of normal (ULN).
- patients with severe renal impairment (creatinine clearance <30 ml/min).
- patients with myopathy.
- patients receiving concomitant cyclosporine.
- during pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.

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

- moderate renal impairment (creatinine clearance < 60 ml/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.
- Asian patients.
- concomitant use of fibrates.

(see WARNINGS AND PRECAUTIONS; DRUG INTERACTIONS; PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES)

WARNINGS AND PRECAUTIONS

Renal effects / proteinuria and hematuria

Proteinuria, detected by dipstick testing and mostly tubular in origin and microscopic hematuria have been reported in patients treated with higher doses of rosuvastatin, in particular 40 mg, where it was transient or intermittent in most cases. Proteinuria has not been reported to be predictive of acute or progressive renal disease (see UNDESIRABLE EFFECTS).

These findings were more frequent in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator HMG-CoA reductase inhibitors, 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.

The reporting rate for serious renal events in post-marketing use is higher at the 40 mg dose. An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

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). As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis associated with rosuvastatin in post-marketing use is higher at the 40 mg dose.

Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in rosuvastatin-treated patients with all doses and in particular with doses > 20 mg. Very rare cases of rhabdomyolysis have been reported with the use of ezetimibe in combination with HMG-CoA reductase inhibitors. A pharmacodynamic interaction cannot be excluded (see DRUG INTERACTIONS) and caution should be exercised with their combined use.

Rosuvastatin should be prescribed with caution in patients with predisposing factors for myopathy (e.g., age ≥ 65 years, inadequately treated hypothyroidism, renal impairment).

Creatine kinase measurement
Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of a plausible alternative cause of CK increase which may confound interpretation of the result. If CK levels are significantly elevated at baseline (>5xULN) a confirmatory test should be carried out within 5 to 7 days. If the repeat test confirms a baseline CK >5xULN, treatment should not be started.

Before treatment
Rosuvastatin, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

• renal impairment
• 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 >65 years
• situations where an increase in plasma levels may occur (see PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES).
• 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 CK levels are significantly elevated at baseline (>5xULN), treatment should not be started.

Whilst on treatment
All patients should be advised to promptly report to their physician inexplicable/unexplained muscle pain, tenderness, cramps or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing rosuvastatin.

CK levels should be measured in these patients. Therapy should be discontinued if CK levels are markedly elevated (>5xULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤ 5xULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing rosuvastatin or an alternative HMG-CoA reductase inhibitor at the lowest dose with close monitoring. Routine monitoring of CK levels in asymptomatic patients is not warranted.

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, lopinavir/ritonavir, or atazanavir/ritonavir.

An increase in the incidence of myositis and myopathy has been reported in patients receiving other HMG-CoA reductase inhibitors together with fibric acid derivatives including gemfibrozil, cyclosporine, nicotinic acid, azole antifungals, protease inhibitors and macrolide antibiotics. Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of rosuvastatin and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of such combinations. The 40 mg dose is contraindicated with concomitant use of a fibrate (see DRUG INTERACTIONS; DOSAGE AND ADMINISTRATION; UNDESIRABLE EFFECTS).

Rosuvastatin therapy should be discontinued if markedly elevated creatine kinase levels occur or myopathy is diagnosed or suspected.

Rosuvastatin should 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 have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin (including rosuvastatin) 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.

Liver effects

As with other HMG-CoA reductase inhibitors, rosuvastatin should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease (including chronic liver disease).

It is recommended that liver function tests be carried out prior to treatment initiation and if signs or symptoms of liver injury occur, and 3 months following the initiation of treatment. Rosuvastatin should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal. The reporting rate for serious hepatic events (consisting mainly of increased hepatic transaminases) in post-marketing use is higher at the 40 mg dose.

Increases in serum transaminases [AST (SGOT) or ALT (SGPT)] including >3 times the upper limit of normal 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. There were two cases of jaundice, for which a relationship to rosuvastatin therapy could not be determined, which resolved after discontinuation of therapy. There were no cases of liver failure or irreversible liver disease.

There have been rare postmarketing 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 with rosuvastatin, promptly interrupt therapy. If an alternate etiology is not found, do not restart rosuvastatin.

In patients with secondary hypercholesterolemia excluding heterozygous familial hypercholesterolemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with rosuvastatin.

Active liver disease, which may include unexplained persistent transaminase elevations, is a contraindication to the use of rosuvastatin (see CONTRAINDICATIONS).

Race

An increase in exposure has been reported in Asian subjects compared with Caucasians (see DOSE AND METHOD OF ADMINISTRATION; CONTRAINDICATIONS; PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES).

Interstitial lung disease

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

Diabetes mellitus / endocrine effects

Some evidence suggests that statins (including rosuvastatin) as a class raise blood fasting serum glucose levels and HbA1c, 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. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI >30 kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Although 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.

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 (see DRUG INTERACTIONS).

Pediatric population

The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in pediatric patients 10 to 17 years of age taking rosuvastatin is limited to a one-year period. No effect on growth, weight, BMI or sexual maturation was reported. The information in children and adolescent patients is limited and the long-term effects of rosuvastatin (>1 year) on puberty are unknown. In children and adolescents receiving rosuvastatin, CK elevations >10xULN and muscle symptoms following exercise or increased physical activity have been reported more frequently compared to observations in adults (see UNDESIRABLE EFFECTS).

Lactose intolerance

This product contains lactose as an excipient. Therefore, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Effects on ability to drive and use machines

The effect of rosuvastatin on the ability to drive and use machines has not been reported. However, 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.

Patient counseling information

Skeletal muscle effects: Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if these muscle signs or symptoms persist after discontinuing rosuvastatin.

Concomitant use of antacids: When taking rosuvastatin with an aluminum and magnesium hydroxide combination antacid, the antacid should be taken at least 2 hours after rosuvastatin administration.
Pregnancy: Rosuvastatin is contraindicated during pregnancy.

Liver enzymes: It is recommended that liver enzyme tests be performed before the initiation of rosuvastatin and if signs or symptoms of liver injury occur. All patients treated with rosuvastatin should be advised to promptly report any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.

USE IN SPECIAL POPULATIONS

Pregnancy

Rosuvastatin is contraindicated in pregnancy. Women of child bearing potential should use appropriate contraceptive measures. Since cholesterol and other products of cholesterol biosynthesis are essential for the development of the fetus, the potential risk from inhibition of HMG-CoA reductase outweighs the advantage of treatment during pregnancy. There is limited evidence of reproductive toxicity in animal. If a patient becomes pregnant during use of this product, treatment should be discontinued immediately (see CONTRAINDICATIONS).

Lactation

Rosuvastatin is contraindicated during lactation and women who require rosuvastatin treatment should be advised not to nurse their infants. Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion in milk in humans (see CONTRAINDICATIONS).

Pediatric use

Rosuvastatin has not been studied in prepubertal patients or patients younger than 10 years of age. Doses of rosuvastatin greater than 20 mg have not been studied in the pediatric population. In children and adolescents with homozygous familial hypercholesterolemia, experience is limited to eight patients (aged 8 years and above).

Geriatric use

No overall differences in safety or effectiveness were reported between elderly (≥ 65 years of age) 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 (see WARNINGS AND PRECAUTIONS).

Renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment. The recommended start dose is 5 mg in patients with moderate renal impairment (creatinine clearance of <60 ml/min). The 40 mg dose is contraindicated in patients with moderate renal impairment. The use of rosuvastatin in patients with severe renal impairment is contraindicated for all doses (see CONTRAINDICATIONS; PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES).

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 (see CONTRAINDICATIONS; WARNING AND PRECAUTIONS).

Asian patients

An approximate 2-fold increase in median exposure to rosuvastatin has been reported in Asian subjects when compared with Caucasian controls. Rosuvastatin dosage should be adjusted in Asian patients (see DOSE AND METHOD OF ADMINISTRATION).

DRUG INTERACTIONS

Cyclosporine

Concomitant use of rosuvastatin with cyclosporine is contraindicated. During concomitant treatment with rosuvastatin and cyclosporine, rosuvastatin AUC values were reported to be higher than those in healthy subjects (see CONTRAINDICATION). Concomitant administration did not affect plasma concentrations of cyclosporine.

Vitamin K antagonists/ coumarin anticoagulants

As with other HMG-CoA reductase inhibitors, the initiation of treatment or dosage up-titration of rosuvastatin in patients treated concomitantly with vitamin K antagonists (e.g. warfarin or another coumarin anticoagulant) may result in an increase in International Normalised Ratio (INR). Discontinuation or down-titration of rosuvastatin may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.

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 (see WARNINGS AND PRECAUTIONS).

Ezetimibe

Concomitant use of rosuvastatin and ezetimibe resulted in increase in AUC of rosuvastatin in hypercholesterolaemic subjects. A pharmacodynamic interaction, in terms of adverse effects, between rosuvastatin and ezetimibe cannot be ruled out (see WARNINGS AND PRECAUTIONS).

Gemfibrozil, niacin, fenofibrates and other lipid-lowering products

Concomitant use of rosuvastatin and gemfibrozil resulted in increase in rosuvastatin C_{max} and AUC (see WARNINGS AND PRECAUTIONS).

Due to reported 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.

No pharmacokinetic relevant interaction with fenofibrate is expected, however a pharmacodynamic interaction may occur.

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 used when prescribing fenofibrates with rosuvastatin.

Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (> or equal to 1g/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. 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 used when prescribing with rosuvastatin. The 40 mg dose is contraindicated with concomitant use of a fibrate (see CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS). These patients should also start with the 5 mg dose.

Protease inhibitors

Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure. The protease inhibitor combinations atazanavir/ritonavir increase rosuvastatin AUC and C_{max}. The concomitant use of rosuvastatin and some protease inhibitor combination may be considered after careful consideration of rosuvastatin dose adjustments based on the expected increase in rosuvastatin exposure (see DOSE AND METHOD OF ADMINISTRATION; WARNINGS AND PRECAUTIONS).

Antacid

The simultaneous dosing of rosuvastatin with an antacid suspension containing aluminium and magnesium hydroxide resulted in a decrease in rosuvastatin plasma concentration. 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 decrease in $AUC_{(0-t)}$ and C_{max} 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. These increased plasma levels should be considered when selecting oral contraceptive doses. There are no reported pharmacokinetic information in subjects taking concomitant rosuvastatin and HRT and therefore a similar effect cannot be excluded. However, the combination has been extensively used in women and was well tolerated.

Other medicinal products / digoxin

No clinically relevant interaction with digoxin is expected.

Cytochrome P450 enzymes

It has been reported 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. No clinically relevant interactions have been reported between rosuvastatin and either fluconazole (an inhibitor of CYP2C9 and CYP3A4) or ketoconazole (an inhibitor of CYP2A6 and CYP3A4).

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.

UNDESIRABLE EFFECTS

The following serious adverse reactions are discussed in greater detail in WARNINGS AND PRECAUTIONS section:

- Rhabdomyolysis with myoglobinuria and acute renal failure, and myopathy (including myositis).
- Liver enzyme abnormalities.

The adverse events reported with rosuvastatin are generally mild and transient. The most commonly reported adverse reactions that led to treatment discontinuation were: myalgia, abdominal pain, hepatic enzyme increased, headache and nausea. The most commonly reported adverse reactions were: headache, myalgia, abdominal pain, asthenia and nausea.

Below given is the summary of adverse events reported with rosuvastatin:

Immune system disorders
Rare: hypersensitivity reactions including angioedema.

Endocrine disorders
Common: diabetes mellitus[1], significantly increased mean HbA1c.
[1] Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥5.6 mmol/L, BMI >30 kg/m^2, raised triglycerides, history of hypertension).

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 with myoglobinuria and acute renal failure.

General disorders
Common: asthenia.

Laboratory abnormalities
Dipstick-positive proteinuria and microscopic hematuria (see WARNINGS AND PRECAUTIONS); elevated creatine phosphokinase, transaminases (including ALT > 3 times upper limit of normal), glucose, glutamyl transpeptidase, alkaline phosphatase, and bilirubin; and thyroid function abnormalities.

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 reported in patients treated with rosuvastatin. Shifts in urine protein from none or trace to ++ or more were reported in some patients

at some time during treatment with 10 and 20 mg and 40 mg. A minor increase in shift from none or trace to + was reported with the 20 mg dose. In most cases, proteinuria decreases or disappears spontaneously on continued therapy. A causal association has not identified between proteinuria and acute or progressive renal disease. Hematuria has been reported in patients treated with rosuvastatin.

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 and in particular with doses > 20 mg. A dose-related increase in CK levels has been reported in patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient. If CK levels are elevated (>5 x ULN), treatment should be discontinued (see WARNINGS AND PRECAUTIONS).

Liver effects: As with other HMG-CoA reductase inhibitors, a dose-related increase in transaminases has been reported in a small number of patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient.
The following adverse events have also been reported:

Nervous system disorders
Very rare: polyneuropathy, memory loss, depression, sleep disorders (including insomnia and nightmares).
Not known: Peripheral neuropathy

Respiratory, thoracic and mediastinal disorders
Not known: cough, dyspnoea.

Gastrointestinal disorders
Not known: diarrhoea.

Hepatobiliary disorders
Very rare: jaundice, hepatitis, fatal and non-fatal hepatic failure.
Rare: increased transaminases.

Skin and subcutaneous tissue disorders
Not known: Stevens-Johnson syndrome.

Musculoskeletal disorders
Very rare: arthralgia.
Not known: immune-mediated necrotising myopathy.
Renal disorders
Very rare: hematuria.

Reproductive system and breast disorders
Very rare: gynecomastia.

General disorders and administration site conditions
Not known: edema.

Blood and lymphatic system disorders
Rare: Thrombocytopenia

There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Increases in HbA1c and fasting blood glucose have been reported with statins. The risk of hypoglycemia, however, is outweighed by the reduction in vascular risk with statins.

The following adverse events have been reported with some statins: Depression, sleep disturbances, including insomnia and nightmares, sexual dysfunction, exceptional cases of interstitial lung disease, especially with long term therapy (see WARNINGS AND PRECAUTIONS), tendon disorders, sometimes complicated by rupture.

The reporting rates for rhabdomyolysis, serious renal events and serious hepatic events (consisting mainly of increased hepatic transaminases) is higher at the 40 mg dose.

Pediatric population

Creatine kinase/phosphokinase elevations >10 x ULN and muscle symptoms following exercise or increased physical activity were reported more frequently in children and adolescents compared to adults (see WARNINGS AND PRECAUTIONS). In other respects, the safety profile of rosuvastatin was similar in children and adolescents compared to adults.

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. Liver function and CK levels should be monitored. Hemodialysis is unlikely to be of benefit.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

Pharmacodynamic properties

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.

Rosuvastatin reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I. Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

A therapeutic effect is obtained within 1 week following treatment initiation and 90% of maximum response is achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

Pharmacokinetic properties

Absorption

The peak plasma concentrations of rosuvastatin are reached 3 to 5 hours following oral dosing. Both peak concentration (C_{max}) and area under the plasma concentration time curve (AUC) increased in approximate proportion to rosuvastatin dose. The absolute bioavailability of rosuvastatin is approximately 20%.

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.

Plasma concentrations of rosuvastatin do not differ following evening or morning drug administration.

Significant LDL-C reductions have been reported when rosuvastatin is given with or without food and regardless of the time of day of drug administration.

Distribution

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% of dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 2C9, and 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 inhibitor activity is accounted by rosuvastatin.

Excretion

Following oral administration, rosuvastatin and its metabolite are primarily excreted in the faeces (90%). The elimination half-life ($t_{1/2}$) of rosuvastatin is approximately 19 hours.

After an intravenous dose, approximately 28% of total body clearance was via the renal route and 72% by the hepatic route.

Special populations

Age and sex
There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin.

Race
An approximate 2-fold elevation in median AUC has been reported in Asian subjects compared with Caucasians. No clinically relevant differences in pharmacokinetics have been reported among Caucasian, Hispanic and Black or Afro-Caribbean groups.

STORAGE
Store below 30^0C, protected from moisture.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN

SUPPLY
Blister of 7's, pack of 4x7's

Information compiled in March 2015

MADE IN INDIA:
RANBAXY LABORATORIES LIMITED
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Himachal Pradesh-173025

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