ROZTOR™– 5/10 TABLETS

PRODUCT DESCRIPTION

ROZTOR™ 5mg/10mg Tablet:

Each film-coated tablet contains,
Rosuvastatin Calcium equivalent to Rosuvastatin – 5mg/10mg

PHARMACOLOGIC PROPERTIES

Mechanism of action

Rosuvastatin is a selective and competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme that converts HMG-CoA to mevalonate, a precursor of cholesterol.

Pharmacodynamics

In vivo studies in animals and *in vitro* studies in cultured animal and 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 low-density lipoprotein (LDL) receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, rosuvastatin inhibits hepatic synthesis of very-low-density lipoprotein (VLDL), which reduces the total number of VLDL and LDL particles. Rosuvastatin reduces elevated LDL-cholesterol (LDL-C), total-cholesterol (total-C) and triglycerides (TG) and increases high-density lipoprotein-cholesterol (HDL-C). It also lowers apolipoprotein (Apo) B, non-HDL-C, VLDL-cholesterol (VLDL-C), VLDL-TG and increases ApoA1. Rosuvastatin also lowers the LDL-C/HDL-C, total-C/HDL-C and non-HDL-C/HDL-C and the ApoB/ApoA1 ratios.

Pharmacokinetics

Absorption

In clinical pharmacology studies, peak plasma concentrations of rosuvastatin were 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 did not affect the AUC of rosuvastatin. The AUC of rosuvastatin does not differ following evening or morning drug administration.

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 (CYP) 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.

Elimination

Following oral administration, 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. The geometric mean plasma clearance is approximately 50 liters/hour (coefficient of variation 21.7%). 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.

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

Linearity*:* Systemic exposure of rosuvastatin increases in proportion to dose. There are no changes in pharmacokinetic parameters following multiple daily doses.

SPECIAL POPULATIONS

Age and sex*:* There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin in adults. The pharmacokinetics of rosuvastatin in children and adolescents with heterozygous familial hypercholesterolaemia was similar to that of adult volunteers.

Race*:* Pharmacokinetic studies show an approximate 2-fold elevation in median AUC and C_{max} in Asian subjects (Japanese, Chinese, Filipino, Vietnamese and Koreans) compared with Caucasians; Asian- Indians show an approximate 1.3-fold elevation in median AUC and C_{max}. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics between Caucasian and Black groups.

Renal insufficiency*:* In a study in subjects with varying degrees of renal impairment, mild to moderate renal disease had no influence on plasma concentration of rosuvastatin or the N-desmethyl metabolite. Subjects with severe impairment (Cr_{Cl} <30 ml/min) had a 3-fold increase in plasma concentration and a 9-fold increase in the N-desmethyl metabolite concentration compared to healthy volunteers. Steady-state plasma concentrations of rosuvastatin in subjects undergoing haemodialysis were approximately 50% greater compared to healthy volunteers.

Hepatic insufficiency*:* In a study with subjects with varying degrees of hepatic impairment there was no evidence of increased exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, two subjects with Child-Pugh scores of 8 and 9 showed an increase in systemic exposure of at least 2-fold compared to subjects with lower Child-Pugh scores. There is no experience in subjects with Child-Pugh scores above 9.

Paediatric population*:* The pharmacokinetic parameters in paediatric patients with heterozygous

familial hypercholesterolaemia (HeFH) aged 10 to 17 years have not been fully characterized. A small pharmacokinetic study with rosuvastatin (given as tablets) in 18 paediatric patients demonstrated that exposure in paediatric patients appears comparable to exposure in adult patients. In addition, the results indicate that a large deviation from dose proportionality is not expected.

Pharmacogenomics

Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, involves organic anion-transporting polypeptide (OATP) 1B1 and other transporter proteins. Higher plasma concentrations of rosuvastatin have been reported in very small groups of patients (n=3 to 5) who have reduced function alleles of the gene that encodes OATP1B1 (*SLCO1B1* 521T>C). The frequency of this genotype (i.e. *SLCO1B1* 521 C/C) is generally lower than 5% in most racial/ethnic groups. The impact of this polymorphism on efficacy and/or safety of rosuvastatin have not been clearly established.

INDICATIONS

Hyperlipidemia and Mixed Dyslipidemia

Rosuvastatin is indicated as adjunctive therapy to diet to reduce elevated total-C, LDL-C, ApoB, non-HDL-C, and TG 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.

Hypercholesterolaemia

Adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia/HeFH) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Pediatric Patients with Familial Hypercholesterolemia

Adjunct to diet to reduce total-C, LDL-C and ApoB levels in children and adolescents:

- Age 8 to 17 years with HeFH 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
- Age 7 to 17 years with homozygous familial hypercholesterolemia (HoFH), either alone or with other lipid- lowering treatments (e.g., LDL apheresis)

Adults with Homozygous Familial Hypercholesterolemia (HoFH)

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 HoFH.

Hypertriglyceridemia

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

Primary Dysbetalipoproteinemia (Type III Hyperlipoproteinemia)

Rosuvastatin is indicated as adjunctive therapy to diet for the treatment of patients with

primary dysbetalipoproteinemia (Type III hyperlipoproteinemia).

Slowing of the Progression of Atherosclerosis

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 Events

Prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors.

In individuals without clinically evident coronary heart disease (CHD) but with an increased risk of Cardiovascular Disease (CVD) based on age ≥50 years old in men and ≥60 years old in women, high-sensitivity C-reactive protein (hsCRP) ≥2 mg/L, and the presence of at least one additional CVD risk factor such as hypertension, low HDL-C, smoking, or a family history of premature CHD, Rosuvastatin is indicated as an adjunct to correction of other risk factors to:

- 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

Before treatment initiation the patient should be placed on a standard cholesterol-lowering diet that should continue during treatment. The dose should be individualized according to the goal of therapy and patient response, using current consensus guidelines. Rosuvastatin may be given at any time of day, with or without food.

The dose range for Rosuvastatin is 5 to 40 mg orally once daily. The usual starting dose is 5-10 mg. Rosuvastatin can be administered as a single dose at any time of day, with or without food. The tablet should be swallowed whole.

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 maximum 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.

Treatment of hypercholesterolaemia

The recommended start dose is 5 mg or 10 mg orally once daily in both statin naive and patients switched from another HMG CoA reductase inhibitor. The choice of start dose should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the

potential risk for adverse reactions (see below). A dose adjustment to the next dose level can be made after 4 weeks, if necessary. The usual starting dose in adult patients with homozygous familial hypercholesterolemia (HoFH) is 20 mg once daily. In light of the increased reporting rate of adverse reactions with a 40 mg dose compared to lower doses, a final titration to the maximum dose of 40 mg should only be considered in patients with severe hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia), who do not achieve their treatment goal on 20 mg, and in whom routine follow-up will be performed. Specialist supervision is recommended when a 40 mg dose is initiated.

Prevention of cardiovascular events

In the cardiovascular events risk reduction study, the dose used was 20 mg daily.

Paediatric population

Paediatric use should only be carried out by specialists.

In HeFH, 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 HoFH, the recommended dose is 20 mg orally once daily in patients 7 to 17 years of age.

Children and adolescents 10 to 17 years of age (boys Tanner Stage II and above, and girls who are at least 1 year post-menarche).

In children and adolescents with heterozygous familial hypercholesterolaemia the usual start dose is 5 mg daily. The usual dose range is 5-20 mg orally once daily. Titration should be conducted according to the individual response and tolerability in paediatric patients, as recommended by the paediatric treatment recommendations. Children and adolescents should be placed on standard cholesterol- lowering diet before rosuvastatin treatment initiation; this diet should be continued during rosuvastatin treatment. Safety and efficacy of doses greater than 20 mg have not been studied in this population.

Children younger than 10 years

Experience in children younger than 10 years is limited to a small number of children (aged between 8 and 10 years) with homozygous familial hypercholesterolaemia. Therefore, Rosuvastatin is not recommended for use in children younger than 10 years.

Geriatric population (Use in the elderly)

A start dose of 5 mg is recommended in patients >70 years. No other dose adjustment is necessary in relation to age.

Dosage in patients with 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. For patients with severe renal impairment (CL_{cr}<30 mL/min/1.73 m^2) not on hemodialysis, dosing of Rosuvastatin should be started at 5 mg once daily and not exceed 10 mg once daily. The use of Rosuvastatin in patients with severe renal impairment is contraindicated for all doses.

Dosage in patients with Hepatic Impairment

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.

Race

Increased systemic exposure has been seen in Asian subjects. The recommended start dose is 5 mg for patients of Asian ancestry. A 40 mg dose is contraindicated in these patients.

Dosage in patients with pre-disposing factors to Myopathy

The recommended start dose is 5 mg in patients with predisposing factors to myopathy. A 40 mg dose is contraindicated in some of these patients

Use with Concomitant Therapy

Patients Taking Cyclosporine: The dose of Rosuvastatin should not exceed 5 mg once daily

Patients taking Gemfibrozil:

Avoid concomitant use of Rosuvastatin with gemfibrozil. If concomitant use cannot be avoided, initiate Rosuvastatin therapy with 5 mg once daily. The dose of Rosuvastatin should not exceed 10 mg once daily

Patients Taking Lopinavir and Ritonavir or Atazanavir and Ritonavir, or Simeprevir:

Initiate Rosuvastatin therapy with 5 mg once daily. The dose of Rosuvastatin should not exceed 10 mg once daily

Genetic Polymorphisms

Specific types of genetic polymorphisms are known that can lead to increased rosuvastatin exposure. For patients who are known to have such specific types of polymorphisms, a lower daily dose of Rosuvastatin is recommended.

CONTRAINDICATIONS

- Patients with hypersensitivity to rosuvastatin or any of the excipients. Hypersensitivity reactions including rash, pruritus, urticaria and angioedema have been reported with rosuvastatin
- Patients with active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels
- Patients with severe renal impairment (creatinine clearance <30 ml/min).
- Patients with myopathy.
- Patients receiving concomitant cyclosporin.
- Women who are pregnant or may become pregnant Nursing mothers

WARNINGS & PRECAUTIONS

Renal Effects

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed 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 shown to be predictive of acute or

progressive renal disease. The reporting rate for serious renal events in post-marketing use is higher at a 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

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. In 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, lopinavir/ritonavir or atazanavir/ritonavir or simeprevir. Cases of myopathy, including rhabdomyolysis have been reported with HMG-CoA reductase inhibitors, including rosuvastatin, co-administered with colchicine, and caution should be exercised when prescribing Rosuvastatin with colchicine.

Rosuvastatin therapy should be discontinued if markedly elevated creatine kinase (CK) 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).

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by proximal muscle weakness and elevated serum CK, 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 physicians unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing Rosuvastatin.

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. It is recommended that liver function tests be carried out prior to, 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 a 40 mg dose.

In patients with secondary hypercholesterolaemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with Rosuvastatin.

Liver Enzyme Abnormalities

It is recommended that liver enzyme tests be performed before the initiation of Rosuvastatin therapy, and if signs or symptoms of liver injury occur. Increases in serum transaminases 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 in these trials.

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 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.

Renal Impairment

Rosuvastatin exposure is not influenced by mild- to moderate renal impairment (CL_{cr}>30 mL/min/1.73 m^2); 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 (CL_{cr} <30 mL/min/1.73 m^2) not requiring hemodialysis. Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of rosuvastatin, in particular 40 mg, where it was transient or intermittent in most cases.

Concomitant Coumarin Anticoagulants

Caution should be exercised when anticoagulants are given in conjunction with rosuvastatin because of the 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.

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

Increases in hemoglobin A1c (HbA1c) and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including rosuvastatin. Based on clinical trial data with rosuvastatin, in some instances, these increases may exceed the threshold for the diagnosis of diabetes mellitus. 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.

Race

Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians.

Protease inhibitors

The concomitant use with protease inhibitors is not recommended.

Lactose intolerance

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. 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

In patients with fasting glucose 5.6 to 6.9mmol/L, treatment with rosuvastatin has been associated with an increased risk of diabetes mellitus.

Females and Males of Reproductive Potential

Contraception

Rosuvastatin may cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ROZTOR.

Pediatric Use

In children and adolescents 8 to 17 years of age with HeFH, the safety and effectiveness of rosuvastatin as an adjunct to diet to reduce total-C, LDL-C, and ApoB levels when, after an adequate trial of diet therapy, LDL-C exceeds 190 mg/dL or when LDL-C exceeds 160 mg/dL and there is a positive family history of premature CVD or two or more other CVD risk factors, were established in one controlled trial and in one open-label, uncontrolled trial. The long-term efficacy of rosuvastatin therapy initiated in childhood to reduce morbidity and

mortality in adulthood has not been established.

The safety and effectiveness of rosuvastatin in patients 10 to 17 years of age with HeFH were evaluated in a controlled clinical trial of 12 weeks duration followed by 40 weeks of open-label exposure. Patients treated with 5 mg, 10 mg and 20 mg daily rosuvastatin had an adverse experience profile generally similar to that of patients treated with placebo. There was no detectable effect of rosuvastatin on growth, weight, body mass index (BMI), or sexual maturation in pediatric patients (10 to 17 years of age).

Rosuvastatin has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age with HeFH. However, the safety and effectiveness of rosuvastatin were evaluated in a two year open-label uncontrolled trial that included children and adolescents 8 to 17 years of age with HeFH. The safety and efficacy of rosuvastatin in lowering LDL-C appeared generally consistent with that observed for adult patients, despite limitations of the uncontrolled study design.

Children and adolescents 7 to 15 years of age with HoFH were studied in a 6-week randomized, placebo-controlled, cross-over study with rosuvastatin 20 mg once daily followed by 12 weeks of open-label treatment. In general, the safety profile in this trial was consistent with that of the previously established safety profile in adults.

Although not all adverse reactions identified in the adult population have been observed in clinical trials of children and adolescent patients, the same warnings and precautions for adults should be considered for children and adolescents. Adolescent females should be counseled on appropriate contraceptive methods while on Rosuvastatin therapy.

Geriatric Use

Of the 10,275 patients in clinical studies with rosuvastatin, 3,159 (31%) were 65 years and older, and 698 (6.8%) were 75 years and older. 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.

Effects on Ability to Drive and Use Machines

Studies to determine the effect of rosuvastatin on the ability to drive and use machines have not been conducted. 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.

DRUG INTERACTIONS

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

Gemfibrozil: Gemfibrozil significantly increased 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.

Protease Inhibitors*:* Co-administration of rosuvastatin with certain protease inhibitors has differing effects on rosuvastatin exposure. Simeprevir, which is a hepatitis C virus (HCV) protease inhibitor, or combinations lopinavir/ritonavir and atazanavir/ritonavir which are HIV-1 protease inhibitors increase rosuvastatin exposure (AUC) up to threefold. For these combinations the dose of Rosuvastatin should not exceed 10 mg once daily. The combinations of tipranavir/ritonavir or fosamprenavir/ritonavir, which are HIV-1 protease inhibitors, produce little or no change in rosuvastatin exposure. Caution should be exercised when rosuvastatin is co-administered with protease inhibitors.

Coumarin Anticoagulants*:* Rosuvastatin significantly increased international normalised ratio (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 lipid- modifying doses (≥1 g/day) of niacin; thus caution should be used when prescribing with Rosuvastatin.

Fenofibrate*:* When rosuvastatin was co-administered with fenofibrate no clinically significant increase in the AUC of rosuvastatin or fenofibrate was observed. 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.

Ezetimibe*:* Concomitant use of 10 mg rosuvastatin and 10 mg ezetimibe resulted in a 1.2 fold increase in AUC of rosuvastatin in hypercholesterolemic subjects. A pharmacodynamic interaction, in terms of adverse effects, between Rosuvastatin and ezetimibe cannot be ruled out.

Colchicine*:* Cases of myopathy, including rhabdomyolysis, have been reported with HMG-CoA reductase inhibitors, including rosuvastatin, co-administered with colchicine, and caution should be exercised when prescribing Rosuvastatin with colchicine.

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 and a 30% decrease in C_{max} of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Vitamin K antagonists*:* 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 INR. Discontinuation or down-titration of rosuvastatin may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.

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.

Fusidic Acid*:* Interaction studies with rosuvastatin and fusidic acid have not been conducted. The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with systemic fusidic acid is necessary, Rosuvastatin should be discontinued throughout the duration of the fusidic acid treatment.

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. No clinically relevant interactions have been observed between rosuvastatin and either fluconazole (an inhibitor of CYP2C9 and CYP3A4) or ketoconazole (an inhibitor of CYP2A6 and CYP3A4). Concomitant administration of itraconazole (an inhibitor of CYP3A4) and rosuvastatin resulted in a 28% increase in AUC of rosuvastatin. This small increase is not considered clinically significant. Therefore, drug interactions resulting from cytochrome P450-mediated metabolism are not expected.

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

PREGNANCY AND LACTATION

Pregnancy Category X

Rosuvastatin is contraindicated in pregnancy and lactation.

Pregnancy

Rosuvastatin is contraindicated in women who are or may become pregnant since safety in pregnant women has not been established and there is no apparent benefit to therapy with rosuvastatin during pregnancy. Because HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from

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

Limited published data on the use of rosuvastatin are insufficient to determine a drug-associated risk of major congenital malformations or miscarriage. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

Lactation

Women of child bearing potential should use appropriate contraceptive measures.

Rosuvastatin use is contraindicated during breastfeeding. Limited data indicate that rosuvastatin is present in human milk. There is no available information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. Because of the potential for serious adverse reactions in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with Rosuvastatin.

ADVERSE EFFECTS

The most commonly reported adverse reactions were:

- Myalgia
- Abdominal pain
- Nausea
- Headache
- Asthenia

Other adverse reactions are dizziness, hypersensitivity (including rash, pruritus, urticaria, and angioedema) and pancreatitis.

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

Endocrine disorders Common: diabetes mellitus
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 and in particular with doses> 20 mg. 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.

Post marketing experience: In addition to the above, the following adverse events have been reported during post marketing experience for ROSUVASTATIN:
Nervous system disorders: Very rare: polyneuropathy, memory loss.
Respiratory, thoracic and mediastinal disorders: Not known: cough, dyspnoea.
Gastrointestinal disorders: Not known: diarrhoea.
Hepatobiliary disorders: Very rare: jaundice, hepatitis; rare: increased transaminases.
Skin and subcutaneous tissue disorders: Not known: Stevens-Johnson syndrome.
Musculoskeletal disorders: Very rare: arthralgia.
Renal disorders: Very rare: haematuria.
General disorders and administration site conditions: Not known: oedema.

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.
- Tendon disorders, sometimes complicated by rupture.
- The reporting rates for rhabdomyolysis, serious renal events and serious hepatic events

(consisting mainly of increased hepatic transaminases) are higher at a 40 mg dose.

The following laboratory abnormalities have also been reported: dipstick-positive proteinuria and microscopic hematuria; elevated CK, transaminases, glucose, glutamyl transpeptidase, alkaline phosphatase, and bilirubin; and thyroid abnormalities.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of rosuvastatin: arthralgia, fatal and non- fatal hepatic failure, hepatitis, jaundice, thrombocytopenia, depression, sleep disorders (including insomnia and nightmares), peripheral neuropathy, interstitial lung disease and gynecomastia. 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. There have been rare reports of immune-mediated necrotizing myopathy associated with statin use.

There have been rare postmarketing 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 non-serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

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.

INCOMPATIBILITY

None

SHELF-LIFE

2 years

STORAGE CONDITION

Protect from light and moisture

PRESENTATION- Rosuvastatin Calcium equivalent to Rosuvastatin – 5mg/10mg tablets

PACKING- 1*10 TAB

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