For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Rosuvastatin Tablets 10 mg & 20 mg

COMPOSITION
Each film coated tablet contains:
Rosuvastatin Ph.Eur……..10 mg & 20 mg

DESCRIPTION
Rosuvastatin is a statin with antilipidemic and potential antineoplastic activities. The chemical name of (E,3R,5S)7[4(4fluorophenyl)2[methyl(methylsulfonyl)amino]-6-propan-2-ylpyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid. The molecular formula $C_{22}H_{28}FN_3O_6S$ .The molecular weight is 481.5 g/mol

PHARMACOLOGICAL CLASSIFICATION
Lipid modifying agents, HMG-CoA reductase inhibitors

PHARMACEUTICAL FORM (DESCRIPTION) OF THE PRODUCT:
Film coated Tablet

PHARMACOLOGICAL ACTION:
Pharmacokinetics

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

Distribution: Rosuvastatin is taken up extensively by the liver which is the primary site of cholesterol synthesis and LDL-C clearance. The volume of distribution of rosuvastatin is approximately 134 L. Approximately 90% of rosuvastatin is bound to plasma proteins, mainly to albumin.

Metabolism: Rosuvastatin undergoes limited metabolism (approximately 10%). *In vitro* metabolism studies using human hepatocytes indicate that rosuvastatin is a poor substrate for cytochrome P450-based metabolism. CYP2C9 was the principal isoenzyme involved, with 2C19, 3A4 and 2D6 involved to a lesser extent. The main metabolites identified are the N-desmethyl and lactone metabolites. The N-desmethyl metabolite is approximately 50% less active than rosuvastatin whereas the lactone form is considered clinically inactive. Rosuvastatin accounts for greater than 90% of the circulating HMG-CoA reductase inhibitor activity.

Excretion: 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 litres/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.

Pharmacodynamices:

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

INDICATIONS AND USAGE

Hyperlipidemia and Mixed Dyslipidemia:

Rosuvastatin is indicated as adjunctive therapy to diet to reduce elevated Total-C, LDL-C, ApoB, nonHDL-C, and triglycerides and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and nonpharmacological interventions alone has been inadequate.

Pediatric Patients with Familial Hypercholesterolemia:

Rosuvastatin is indicated as an adjunct to diet to reduce Total-C, LDL-C and ApoB levels in children and adolescents 8 to17 years of age with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present: LDL-C >190 mg/dL, or >160 mg/dL along with a positive family history of premature cardiovascular disease (CVD) or two or more other CVD risk factors. Reduce LDL-C, Total-C, nonHDL-C and ApoB in children and adolescents 7 to 17 years of age with homozygous familial hypercholesterolemia, either alone or with other lipidlowering treatments (e.g., LDL apheresis).

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 an adjunct to diet for the treatment of adult patients with primary dysbetalipoproteinemia (Type III Hyperlipoproteinemia).

Adult Patients with Homozygous Familial Hypercholesterolemia

Rosuvastatin is indicated as adjunctive therapy to other lipid-lowering treatments (e.g., LDL apheresis) or alone if such treatments are unavailable to reduce LDL-C, Total-C, and ApoB in adult patients with homozygous familial hypercholesterolemia.

Slowing of the Progression of Atherosclerosis

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

Primary Prevention of Cardiovascular Disease

In individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease based on age ≥50 years old in men and ≥60 years old in women, hsCRP ≥2 mg/L, and the presence of at least one additional cardiovascular disease risk factor such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease, rosuvastatin is indicated to:

- reduce the risk of stroke
- reduce the risk of myocardial infarction
- reduce the risk of arterial revascularization procedures

Limitations of Use

Rosuvastatin has not been studied in Fredrickson Type I and V dyslipidemias.

CONTRAINDICATIONS
Rosuvastatin is contraindicated:
- in patients with hypersensitivity to rosuvastatin or to any of the excipients.
- in 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).
- In patients with severe renal impairment (creatinine clearance <30 ml/min).
- In patients with myopathy.
- In patients receiving concomitant ciclosporin.
- 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.

ADVERSE REACTION
The frequencies of adverse reactions are ranked according to 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).

System organ class	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders			Thrombocytopenia		
Immune system disorders			Hypersensitivity reactions including angioedema		
Endocrine disorders	Diabetes mellitus				
Psychiatric disorders					Depression
Nervous system disorders	Headache Dizziness			Polyneuropathy Memory loss	Peripheral neuropathy Sleep disturbances (including insomnia and nightmares)
Respiratory, thoracic and mediastinal disorders					Cough Dyspnoea
Gastro-intestinal disorders	Constipation Nausea Abdominal pain		Pancreatitis		Diarrhoea
Hepatobiliary disorders			Increased hepatic transaminases	Jaundice Hepatitis	
Skin and subcutaneous tissue disorders		Pruritus Rash Urticaria			Stevens-Johnson syndrome
Musculo-skeletal and connective tissue disorders	Myalgia		Myopathy (including myositis) Rhabdomyolysis Lupus-like syndrome Muscle rupture	Arthralgia	Tendon disorders, sometimes complicated by rupture Immune-mediated necrotising myopathy
Renal and urinary disorders				Haematuria	
Reproductive system and breast disorders				Gynaecomastia	
General disorders and administration site conditions	Asthenia				Oedema

Postmarketing Experience:
The following adverse reactions have been identified during postapproval use of rosuvastatin:
Arthralgia, fatal and non-fatal hepatic failure, hepatitis, jaundice, thrombocytopenia, depression, sleep disorders (including insomnia and nightmares), peripheral neuropathy 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 nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

DOSAGE

General Dosing Information:
The dose range for rosuvastatin in adults is 5 to 40 mg orally once daily. The usual starting dose is 10 to 20 mg once daily. The usual starting dose in adult patients with homozygous familial hypercholesterolemia is 20 mg once daily. The maximum 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

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

Dosing in Asian Patients:
In Asian patients, consider initiation of rosuvastatin therapy with 5 mg once daily due to increased rosuvastatin plasma concentrations. The increased systemic exposure should be taken into consideration when treating Asian patients not adequately controlled at doses up to 20 mg/day

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 at 5 mg once daily. the dose of rosuvastatin should not exceed 10 mg once daily patients taking atazanavir and ritonavir, lopinavir and ritonavir, or simeprevir initiat rosuvastatin therapy with 5 mg once daily. the dose of rosuvastatin should not exceed 10 mg once daily

Dosing in patients with severe 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

DRUG INTERACTIONS

Combinations contraindicated

Transporter protein inhibitors: Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of Rosuvastatinwith medicinal products that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy

Ciclosporin: During concomitant treatment with Rosuvastatin and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers Rosuvastatinis contraindicated in patients receiving concomitant ciclosporin Concomitant administration did not affect plasma concentrations of ciclosporin.

Protease inhibitors: Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure

Gemfibrozil and other lipid-lowering products Concomitant use of Rosuvastatinand gemfibrozil resulted in a 2-fold increase in rosuvastatin C_{max} and AUC

Based on data from specific interaction studies no pharmacokinetic relevant interaction with fenofibrate is expected, however a pharmacodynamic interaction may occur. Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (> or equal to 1 g/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 40 mg dose is contraindicated with concomitant use of a fibrate . These patients should also start with the 5 mg dose

Combination not advised

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

Antacid: The simultaneous dosing of Rosuvastatinwith 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.

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

Combinations which need precautions of use

Vitamin K antagonists: As with other HMG-CoA reductase inhibitors, the initiation of treatment or dosage up-titration of Rosuvastatinin 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 Rosuvastatinmay result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.

Oral contraceptive/hormone replacement therapy (HRT): Concomitant use of Rosuvastatinand 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 Rosuvastatinand HRT, therefore, a similar effect cannot be excluded. However, the combination has been extensively used in women in clinical trials and was well tolerated.

Combinations to consider

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

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 treatment should be discontinued throughout the duration of the fusidic acid treatment.

Paediatric population: Interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known.

WARNINGS & PRECAUTIONS

Skeletal Muscle Effects

Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including rosuvastatin. These risks can occur at any dose level, but are increased at the highest dose (40 mg).

Rosuvastatin should be prescribed with caution in patients with predisposing factors for myopathy (e.g., age ≥65 years, inadequately treated hypothyroidism, renal impairment). The risk of myopathy during treatment with rosuvastatin may be increased with concurrent administration of some other lipid-lowering therapies (fibrates or niacin), gemfibrozil, cyclosporine, atazanavir/ritonavir, lopinavir/ritonavir, or simeprevir 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

Rosuvastatin therapy should be discontinued if markedly elevated creatine kinase levels occur or myopathy is diagnosed or suspected. Rosuvastatin therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures).

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 creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

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

Liver Enzyme Abnormalities:

It is recommended that liver enzyme tests be performed before the initiation of rosuvastatin, and if signs or symptoms of liver injury occur.

Increases in serum transaminases [AST (SGOT) OR ALT (SGPT)] have been reported with HMG-COA reductase inhibitors, including rosuvastatin. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. 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 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.

Rosuvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of chronic liver disease Active liver disease, which may include unexplained persistent transaminase elevations, is a contraindication to the use of rosuvastatin.

Concomitant Coumarin Anticoagulants:

Caution should be exercised when anticoagulants are given in conjunction with rosuvastatin because of its potentiation of the effect of coumarin-type 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 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.

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 foetus, the potential risk from inhibition of HMG-CoA reductase outweighs the advantage of treatment during pregnancy. Animal studies provide limited evidence of reproductive toxicity. If a patient becomes pregnant during use of this product, treatment should be discontinued immediately.

Lactation: Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion in milk in humans.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenicity potential. Specific tests for effects on hERG have not been evaluated. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels were as follows: In repeated-dose toxicity studies histopathologic liver changes likely due to the pharmacologic action of rosuvastatin were observed in mouse, rat, and to a lesser extent with effects in the gall bladder in dogs, but not in monkeys. In addition, testicular toxicity was observed in monkeys and dogs at higher dosages. Reproductive toxicity was evident in rats, with reduced litter sizes, litter weight and pup survival observed at maternally toxic doses, where systemic exposures were several times above the therapeutic exposure level.

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. Haemodialysis is unlikely to be of benefit.

EFFECTS ON ABILITY TO DRIVE A 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.

LIST OF EXCIPIENTS

Microcrystalline Cellulose, Lactose Monohydrate, Anhydrous Dibasic Calcium Phosphate, Hypromellose, Crospovidone, Magnesium Stearate, Opadry Pink 03K540028 & Purified water

SHELF-LIFE:

3 years

STORAGE

Store below 30°C in a dry place.
Protect from light.

PRESENTATION

Blister pack of 7 tablets

MACLEODS

MANUFACTURED BY

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DATE OF PREPARATION OF PRESCRIBING INFORMATION:

31/08/2019